

4160-01-P

DMB

Display Date	11-23-98
Publication Date	12-1-98
Certifier	[Signature]

11.08
am

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 208, 314, and 601, and 610

[Docket No. 93N-0371]

RIN 0910-AA37

Prescription Drug Product Labeling; Medication Guide Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is establishing requirements for the distribution of patient labeling for selected prescription human drug and biological products used primarily on an outpatient basis. The agency is requiring the distribution of patient labeling, called Medication Guides, for certain products that pose a serious and significant public health concern requiring distribution of FDA-approved patient medication information. The intent of this action is to improve public health by providing information necessary for patients to use their medications safely and effectively. FDA believes that this program will result in direct improvements in the safe and effective use of prescription medications.

DATES: This regulation is effective (insert date 180 days after date of publication in the FEDERAL REGISTER.) Written comments on the information collection requirements should be submitted by (insert date 60 days after date of publication in the FEDERAL REGISTER.)

ADDRESSES: Submit written comments on the information collection requirements to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Nancy M. Ostrove,
Center for Drug Evaluation and Research (HFD-40),
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD 20857,
301-827-2828,
(Ostrove@CDER.FDA.GOV).

Toni M. Stifano,
Center for Biologics Evaluations and Research (HFM-20),
Food and Drug Administration,
1401 Rockville Pike,
Rockville, MD 20852,
301-827-3028,
(Stifano@A1.CBER.FDA.GOV).

SUPPLEMENTARY INFORMATION:

I. Background

In the FEDERAL REGISTER of August 24, 1995 (60 FR 44182), FDA published a proposed rule entitled, "Prescription Drug Product Labeling; Medication Guide Requirements," under which the agency would encourage development and distribution of written

patient medication information by the private sector. This information was intended to supplement oral counseling from health care professionals. The agency proposed distribution goals and performance standards for this information. The agency proposed to survey the marketplace in the years 2000 and 2006 to determine how much patient medication information is being distributed and whether it is useful. The 1995 proposal sought comment on two approaches FDA could take if the private sector's voluntary program failed to reach the predetermined goals.

The proposal also included provisions that would permit the agency to require FDA-approved written patient information (Medication Guides) for distribution with prescription drug and biological products that pose a "serious and significant public health concern requiring immediate distribution of FDA-approved patient medication information." (For the purposes of this document, the shorter term "serious and significant concern" will be used to refer to those drug products that FDA determines require Medication Guides for safe and effective use by the public.) The agency indicated that it would use this authority only on limited occasions.

In the proposal, FDA stated its position that patient information about the risks and benefits of prescription drug and biological products is necessary for patients to use these products safely and effectively. The overall patient medication information program was proposed to provide patients with the information needed to improve their use of prescription drug and

biological products. Furthermore, FDA demonstrated in the preamble to the proposed rule that the program could result in substantial health care cost savings by reducing the harm caused by inappropriate drug use and enhancing the benefits of drugs by facilitating their proper use.

FDA originally provided 90 days for public comment, and, in response to requests, extended the comment period for an additional 30 days until December 22, 1995 in the FEDERAL REGISTER of November 24, 1995 (60 FR 58025). In the FEDERAL REGISTER of January 30, 1996 (61 FR 2971), the agency announced a public workshop to be held on February 14 and 15, 1996, to discuss issues related to defining the useful information that would be provided in the voluntary program. The agency also sought written comments on issues raised at the workshop. Comments were accepted until March 6, 1996.

As the agency was reviewing these and other comments on the proposed rule, Congress enacted legislation regarding patient labeling. This legislation, section 601 of the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, for the fiscal year ending September 30, 1997 (Pub. L. 104-180) (the Appropriations Act), established a voluntary private-sector process under which national organizations representing health care providers, consumers, pharmaceutical companies, and other interested parties were to collaborate in the development of a long-range plan to achieve the goals of FDA's proposed rule concerning patient labeling as

previously described. The legislation adopted the distribution and information quality goals of the proposed rule. The law further required that the plan developed by these organizations be submitted to the Secretary of Health and Human Services (the Secretary) for acceptance, rejection, or modification before implementation. The collaborative process established by this legislation has been completed and the long-range private-sector plan has been accepted by the Secretary.

While section 601 of the Appropriations Act limits the authority of the Secretary to implement FDA's proposed rule regarding written information voluntarily provided to consumers, there is specific legislative history that makes it clear that section 601 does not preclude FDA from using its existing authority to implement a mandatory program for the small number of products that pose a "serious and significant concern" and require distribution of patient information. That legislative history states that section 601:

[i]s not to be construed as prohibiting the FDA from using its existing authority or regulatory authority to require as part of the manufacturers' approved product labeling the dispensing of written information inserts to consumers on a case-by-case basis with select prescription drugs to meet certain patient safety requirements.

Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Bill, 1997, S. Rept. 104-317, 104th Cong., 2d sess., p. 132, July 11, 1996.

In light of this legislation, the agency is deleting the provisions of the proposed rule that dealt with the private sector voluntary program, and is limiting this final rule to the mandatory program covering products of "serious and significant concern." Because the voluntary program is not part of this final rule, the agency will not summarize and respond to comments relating only to those provisions. Instead, this document will focus on the comments concerning the program for products of "serious and significant concern."

The final rule incorporates most of the provisions of the proposed rule regarding the mandatory program for products of "serious and significant concern" and provides additional clarification regarding how the agency would identify products that require a Medication Guide. Additional changes have been made that reflect the narrowed focus of the final rule. Highlights of the final rule are summarized, followed by a summary and discussion of the comments.

II. Highlights of the Final Rule

The final rule establishes a patient medication information program under which Medication Guides will be required for a small number of products that FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information necessary for the product's safe and

effective use. FDA anticipates that an average, no more than 5 to 10 products per year would require such information.

The major provisions of the medication information program for products of "serious and significant concern" and the changes from the proposed rule follow.

A. General Provisions (Part 208, Subpart A)

1. Scope and Purpose

A number of changes have been made to the provisions in part 208 (21 CFR part 208) to reflect the narrowed focus of this final regulation in response to section 601 of the Appropriations Act, and to clarify its purpose and scope. Section 208.1(a) has been changed to indicate that the final regulation does not cover voluntarily distributed patient information for most prescription drugs, but rather covers products of "serious and significant concern." The phrase "that FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information" was added to § 208.1(a) to accomplish this change.

Section 208.1(a) of the 1995 proposed rule stated that the requirements applied to products "administered primarily on an outpatient basis without direct supervision by a health professional." FDA has changed the term "administered" in this context to the term "used," because "administered" is likely to be misinterpreted as involving administration by another individual. In addition, the agency has determined that Medication Guides may, on rare occasions, be required for

products of "serious and significant concern" that are used on an inpatient basis or under the supervision of a health professional. This change has been made by moving the word "primarily" to immediately follow the word "applies" in the second sentence of § 208.1(a). In light of this change, the last sentence of proposed § 208.1(a) has been deleted, because it is no longer needed.

Under the proposed rule, the patient information program applied to all new prescriptions, but only upon request by the patient for refill prescriptions. Because of the narrowed focus of this final rule and because the agency believes that the patient information that will be provided in Medication Guides is important to the safe and effective use of a product, it is necessary to require the distribution of a Medication Guide with every prescription for that product. Accordingly, § 208.1(a) has been changed so that patient information required under this part must be provided for all prescriptions of the drug, whether they are new prescriptions or refills and regardless of whether the information is requested by the patient.

Section 208.1(b) as proposed has been deleted because the final regulation no longer covers voluntarily distributed patient information. This change was made because of the enactment of section 601 of the Appropriations Act, which created a process under which national organizations representing consumers, health professionals, pharmaceutical companies, and others developed a

plan for the voluntary distribution of patient information. This legislation specifically prohibits the implementation of the proposed rule if a plan acceptable to the Secretary is developed and submitted within the statutory time period. The accompanying legislative history makes it clear, however, that the agency was not precluded from requiring FDA-approved patient leaflets for drugs of serious and significant concern under its existing authority. New § 208.1(b) describes the purpose of patient labeling required under the final regulation.

The information will be required if the agency determines that it is necessary to patients' safe and effective use of the drug product. The agency added this provision to clarify the regulations when it will require Medication Guides and to reflect the agency's intention to make the decision to require a Medication Guide carefully and on a case-by-case basis. This approach to Medication Guides is consistent with the legislative history of the Appropriations Act discussed earlier in this preamble. The new language in § 208.1(b) also helps differentiate required Medication Guides from the voluntary private sector program.

Section 208.1(c) as proposed has been deleted. Its primary purpose was to provide a standard against which voluntarily distributed patient information would be evaluated. However, the voluntary program is no longer part of this regulation. The agency believes that the substance of this provision is valuable, however, and has therefore changed § 208.20, Content and format of a Medication Guide, to include all of the elements of proposed

§ 208.1(c). These elements are also closely related to the criteria adopted during the collaborative private-sector process.

New § 208.1(c) of the final rule describes when FDA may require a Medication Guide. Patient labeling will be required if the agency determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. FDA believes that these circumstances will apply to a very small group of products. These circumstances have been clarified to address comments that they were overly broad.

Proposed § 208.1(d) has been deleted as unnecessary because the final regulation applies only to "serious and significant" products.

2. Definitions

Section 208.3 contains definitions of important terms used in part 208. Several changes have been made in this section to help clarify the Medication Guide program. Numerous comments conveyed confusion about what constitutes a "Medication Guide," for example, whether the term refers to voluntary private sector

patient information or mandated FDA-approved patient information. Therefore, in the final rule new § 208.3(h) defines "Medication Guide" to mean FDA-approved patient labeling conforming to the specifications set forth in part 208 and other applicable regulations. This term now applies only to patient information required for products of "serious and significant concern."

The agency on its own initiative added new § 208.3(e) to include a definition of the term "drug product." The purpose of adding this new definition is to make it clear that the term, as it is used in this final regulation, applies to the finished dosage form of both drug and biological products. Because of the addition of this definition, the subsequent provisions in § 208.3 have been renumbered.

In preparing the final rule, the agency revised the definition of the "manufacturer" of a drug product to be consistent with the definition of the "manufacturer" of a biological product. The definition of a "manufacturer" in the proposed rule inadvertently referred only to the person who actually produced the drug product, while the definition for biologicals included both the actual producer of the product as well as the person who is an applicant for a license where the applicant is responsible for complying with the product and establishment standards. This latter meaning of the term corresponds most closely to the definition of an "applicant" as that term is used in the new drug regulations in part 314 (21 CFR part 314). Therefore, FDA has included the definition of

"applicant" in § 314.3(b) in the definition of a drug product manufacturer in § 208.3(g). It is important for two reasons that both meanings of "manufacturer" be included in the definition of the term for purposes of this final rule. First, FDA intends that each person potentially or actually in the chain of distribution of a product be subject to the distribution requirements in § 208.24 and for that reason both the producer of the product and the person responsible for the product application must be included. Second, for purposes of identifying the person who is responsible for the content and format requirements in § 208.20 and the requirement of obtaining FDA approval of the Medication Guide in § 208.24(a), the agency wishes to clarify that it is the person who is responsible for the product application.

The agency has also added a definition of the term "packer" in new § 208.3(i). Packers are subject to the provisions of this final rule and a definition was needed to distinguish a packer from a manufacturer or distributor.

Section 208.3(k) of this final regulation provides a definition of the terms "serious risk" and "serious adverse effect" that states that these terms mean an adverse drug experience, or the risk of such an experience, as that term is defined elsewhere in the regulations governing drug and biological products. The purpose of adding this definition is to further narrow the scope of this regulation in response to many comments complaining of the breadth of the agency's proposed

criteria for identifying products of "serious and significant concern." (See previous discussion of § 208.1(b) and (c).)

B. General Requirements for a Medication

Guide (Part 208, Subpart B)

1. Content and Format of a Medication Guide

Section 208.20 now contains the requirements for both the content and format of Medication Guides. This section sets forth the specific categories of information about a product that a Medication Guide shall contain, as well as statements that shall appear on a Medication Guide. The agency has generally retained from the proposal the text and order of the headings under which the information shall appear and has also now grouped the information under the appropriate heading. This section also includes specifications for minimum letter height or type size, legibility, and presentation considerations. The combined provision is more concise and the reorganization makes the requirements clearer. The agency notes that the content and format criteria in the final rule are virtually the same as those adopted in the private sector plan discussed earlier.

The order specified in § 208.20(b) starts with a presentation of the most important information patients should know about the product to use it safely and effectively, i.e., why the product poses a serious and significant public health concern requiring distribution of FDA-approved written patient information. This section is being included in place of the summary section originally proposed by FDA. The agency made this

change because it believes that it is redundant to include in such a short document a summary section containing information elaborated in other sections.

This section is followed by sections addressing the product's indications for use, contraindications, directions for use, precautions, and possible side effects. The final rule does not specify where in this order other information (e.g., storage instructions and specific instructions for using products that are not orally administered (e.g., injectables, patches)) may be placed. As reflected in § 208.20(b)(9), the rule permits the insertion of additional headings or subheadings as appropriate for specific Medication Guides.

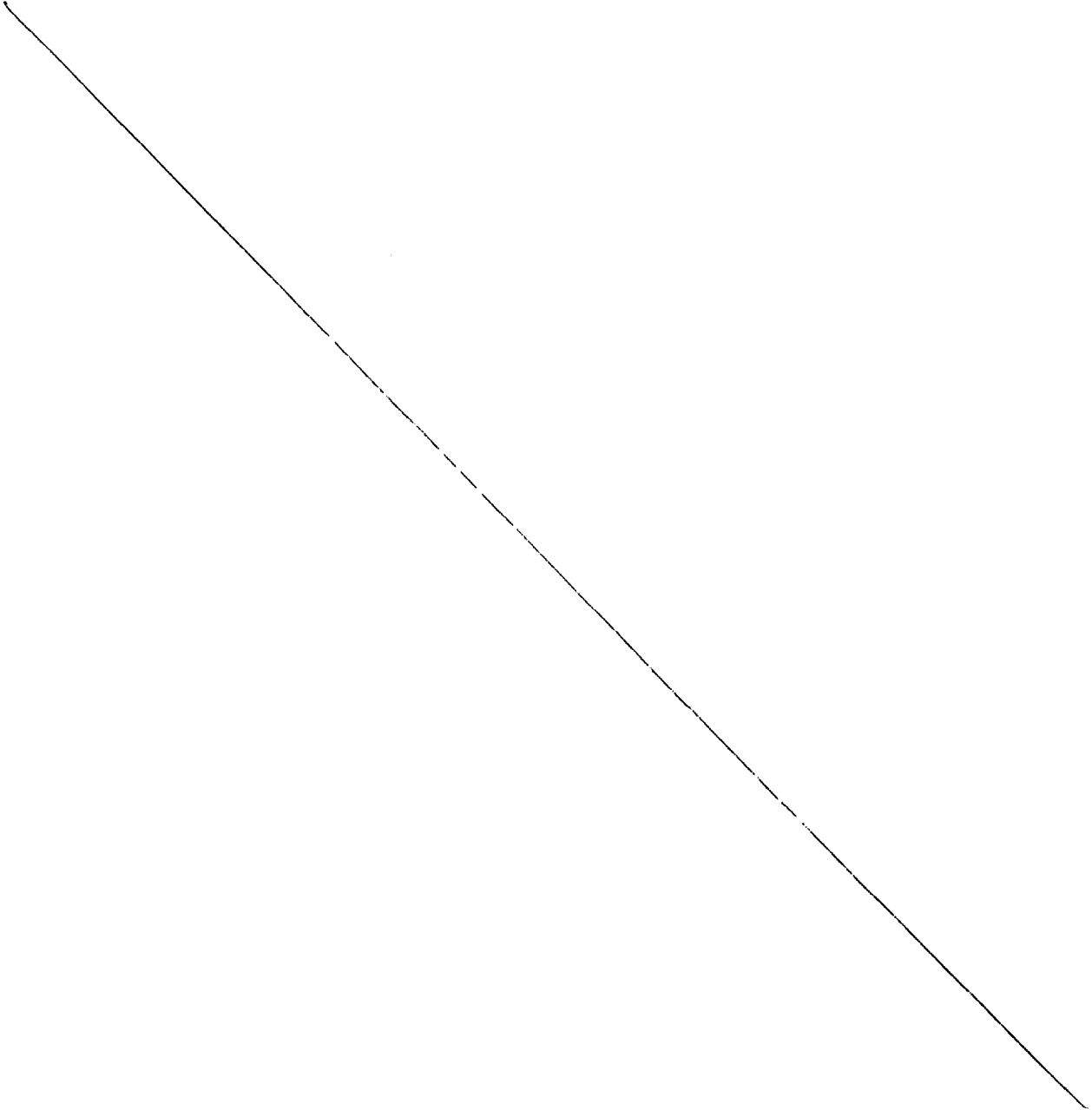
Other changes have been made in § 208.20 of the final rule. As mentioned above, the agency believes that the criteria for determining useful information that were proposed in § 208.1(c) are important and has retained them in the final rule. All of the criteria that Medication Guides must meet, however, are now contained in a single section of this final rule (§ 208.20(a)).

The agency on its own has added language to § 208.20(a)(2) to reinforce the fact that a Medication Guide, while based on the approved labeling, should be understandable to laypersons and therefore need not use the identical language in the approved labeling.

Other small changes have been made in § 208.20 as well. Section 208.20(a)(7) and (b)(1) now require that a Medication Guide contain the established or proper name of the drug in order

14a

to recognize the terminology used for biologicals. (See 21 CFR 600.3(k)). The introductory sentence of § 208.20(b) has been



changed to make it clear that only the headings that have relevance to the drug product should be included in a Medication Guide. Other changes have been made throughout § 208.20(b) to emphasize that only specific, important information about the drug product should be included in a Medication Guide. These changes are being made so that the effectiveness of the patient labeling is not reduced by its being too long or including irrelevant information.

FDA has added the following language to § 208.20(b)(3) relating to the product's indications: "In appropriate circumstances, this section may also explain the nature of the disease or condition the drug product is intended to treat, as well as the benefit(s) of treating the condition." This addition is designed to allow, when relevant, a fuller discussion that could include the benefits of treatment.

Finally, FDA has made two changes to § 208.20(b)(8). First, § 208.20(b)(8)(ii) has been changed to make it clear that a Medication Guide must contain a statement that a drug product should not be used for a condition other than that for which it is prescribed. This change is made to avoid any confusion with the statement that drugs may sometimes be prescribed for uses not described in the Medication Guide. Second, § 208.20(b)(8)(iii) has been changed to make it clear that the name and address of the dispenser may be included in a Medication Guide. The name and address of the manufacturer, distributor, or packer of a drug product that is not also a biological product or of the

manufacturer or distributor of a drug product that is also a biological product is required. This change was made to correct a drafting error in proposed § 208.20(b)(8)(iii) that would have allowed the dispenser's name alone to appear on a Medication Guide.

2. Distributing and Dispensing a Medication Guide

Section 208.24 sets forth the requirements for distributing and dispensing Medication Guides. The agency has made several changes to this section to make clear the responsibilities of each person distributing a drug product subject to this part. The agency has added new § 208.24(a) that explicitly requires the manufacturer to obtain FDA approval of the Medication Guide before it can be distributed. Although this requirement had been stated indirectly in the proposed rule regarding products of "serious and significant concern," the agency believed it should be stated clearly in the final rule. Because the majority of Medication Guides will be required at the time of approval, it is appropriate for FDA to approve the text of both patient labeling and professional labeling at the same time.

Section 208.24(b) states the manufacturer's basic responsibility for ensuring that Medication Guides are available for distribution to patients. Under § 208.24(b), a manufacturer shall provide to distributors, packers, or authorized dispensers to which it ships the drug product, either Medication Guides in sufficient numbers, or the means to produce Medication Guides in sufficient numbers, to permit the authorized dispenser to provide

a Medication Guide to each patient who receives a prescription for the drug product. The agency generally expects that the "means to produce" shall include a computer file of the Medication Guide for use with a computerized patient medication information program. Section 208.24(c) states the responsibility of the distributor or packer that receives Medication Guides, or the means to produce Medication Guides, to provide them to each authorized dispenser to whom it ships a container of drug product.

FDA has changed § 208.24 in several places to make it clear that packers are covered by this final regulation. It appears that packers had been inadvertently omitted from the proposal. The change is intended to make it clear that, in situations where a Medication Guide is distributed with the product, each person in the distribution chain has the responsibility of ensuring that the Medication Guide remains with the product so that it can reach the authorized dispenser.

FDA has also deleted the phrase "finished dosage form" from several places in § 208.24 of this rule. This phrase is no longer needed because the agency has added a definition of "drug product" in § 208.3(e) that clarifies that the term refers to products in finished dosage form.

Section 208.24 has been changed in several places to reflect the fact that Medication Guides must be dispensed with every prescription for a drug product subject to this part, and not just with new prescriptions or if requested by a patient for a

refill prescription. This change is needed because it will be necessary for patients to have the information in a Medication Guide in order to use a product of "serious and significant concern" safely and effectively. It is therefore important for patients to receive this information each time they obtain the drug product.

Some comments noted that dispensers may not know if Medication Guides are provided with the product, affixed on the container, or contained within the package. Therefore, in the final rule, a new § 208.24(d) has been created that states that the label of each container of drug product (which now, because of the added definition of drug product, includes both large volume containers of finished dosage form and unit-of-use containers) shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. This new section also requires that these statements be made in a prominent and conspicuous manner. The agency on its own initiative has amended both § 208.24(d) and the regulations governing labeling of biological products to make clear how manufacturers can comply with the requirements of § 208.24(d) if a container label is too small for the required statement. (See § 610.60(a)(7).)

Section 208.24(c) of the proposed rule required the manufacturer and distributor to provide a Medication Guide with each unit-of-use container intended to be dispensed to a patient.

FDA has omitted this paragraph from the final rule. This provision is not necessary because the responsibility to provide Medication Guides to the authorized dispenser is clear from the other changes to § 208.24. Further, FDA wishes to provide manufacturers, distributors, and packers flexibility in the ways that they can meet that responsibility. If a manufacturer chooses to provide Medication Guides electronically for a product in a unit-of-use container, they may now do so because of this change.

Proposed § 208.24(d) stated that the requirements of part 208 could be met by the manufacturer, distributor, or any other person acting on behalf of the manufacturer or distributor. This section further provided that a manufacturer or distributor could satisfy the requirements of part 208 with a Medication Guide printed by a distributor or authorized dispenser. This provision was intended to enable manufacturers and distributors to make use of third-party information systems that could simplify the process of dispensing patient information leaflets to patients. The proposal envisioned that third parties would most likely both create and distribute Medication Guides to authorized dispensers under the voluntary private-sector program. Proposed § 208.24(d) has been deleted from this final rule. The agency believes that it is no longer necessary because the final rule applies only to Medication Guides for products of "serious and significant concern" that will be approved by the agency and will be part of these products' approved labeling.

Section 208.24(f) was modified in response to several comments. A change has been made to make it clear that wholesalers, as well as authorized dispensers, are not subject to section 510 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360) that requires registration of producers of drugs and listing of drugs in commercial distribution if they change the container, wrapper, or labeling of any drug product, as long as the change is due solely to an act performed under part 208.

3. Exemptions and Deferrals

Section 208.26 provides the circumstances under which there may be exemptions from, or deferrals of, content and format requirements for Medication Guides, and exemption from the distribution of Medication Guides to patients under certain circumstances.

Proposed § 208.26(b) provided, in part, that a licensed practitioner or an authorized dispenser could determine that it is not in the best interests of a patient to receive a Medication Guide. FDA has changed this provision to allow only the licensed practitioner who prescribes a drug product to direct that a Medication Guide be withheld from a patient.

Section 208.26(b) has also been modified to address concerns about possible perceived interference by FDA in the judgments of health care professionals with respect to withholding a Medication Guide from a patient. The final rule does not contain the proposed sentence that would have required authorized dispensers to provide Medication Guides for a particular product

under all circumstances. Consequently, only the patient, and not FDA, can overrule the licensed practitioner's decision to withhold a Medication Guide from that patient.

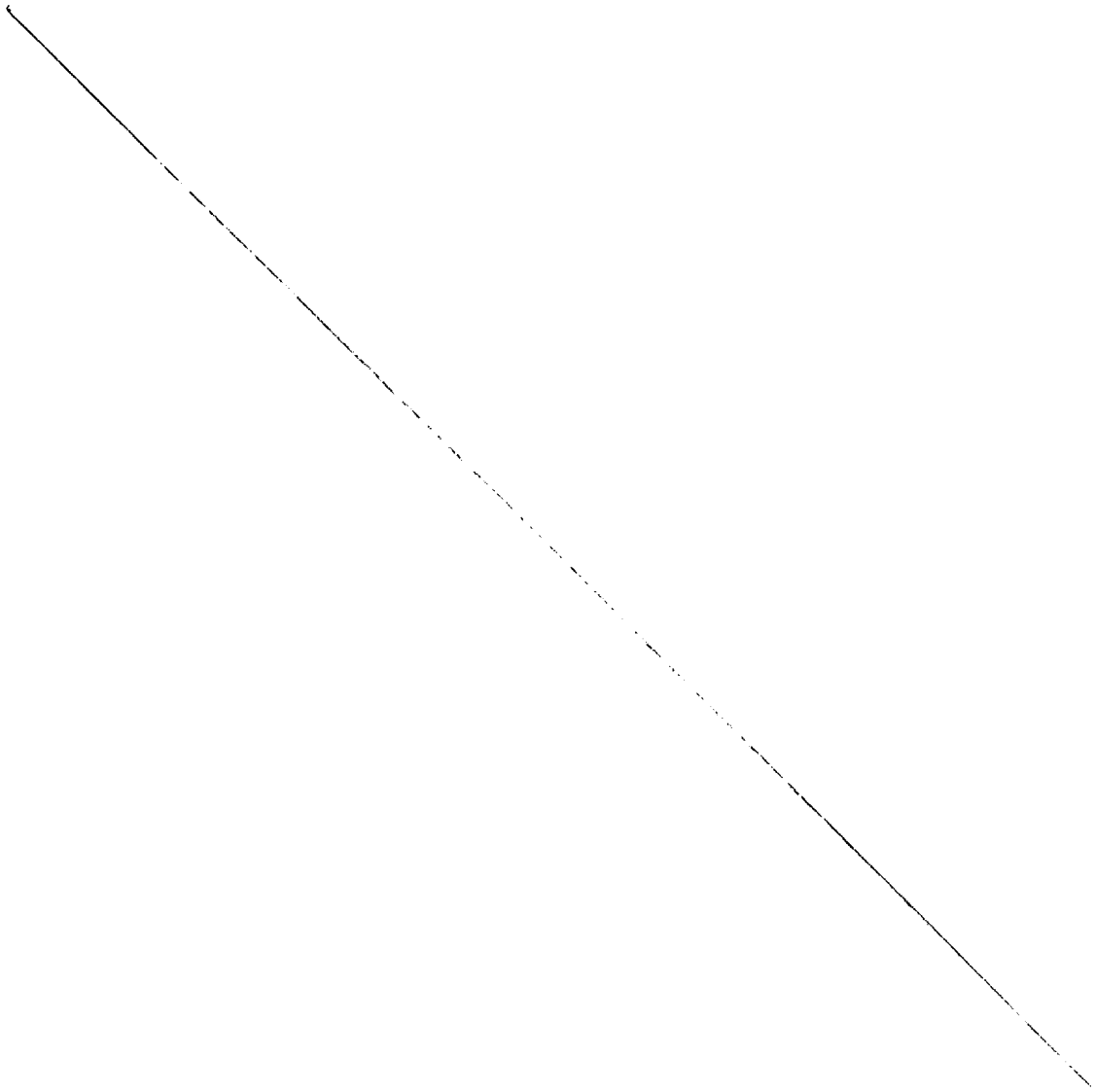
Section 208.26(c) as proposed provided that a Medication Guide was not required to be dispensed in an emergency, or where the manufacturer, distributor, or authorized dispenser did not have a Medication Guide available and could document a good faith effort to provide one. Section 208.26(d) as proposed set forth a small business exemption for certain authorized dispensers. However, this exemption only applied to the broad comprehensive program of distribution of patient information. It did not apply to Medication Guides for products of "serious and significant" concern.

The agency has deleted both proposed § 208.26(c) and (d) from this final rule. FDA does not believe that such exemptions are appropriate for Medication Guides that are required for a very small number of products of "serious and significant concern" and that provide information necessary to the safe and effective use of the product.

III. Comments on the Proposed Rule

FDA received approximately 100 comments in response to the 1995 proposed rule and the request for comments associated with the February 1996 public workshop. The comments came from individual consumers and consumer organizations, academics, individual pharmacists, physicians, and other health care professionals, health professional associations, trade

associations, and prescription drug and biological product manufacturers, attorneys, and others. A number of comments submitted examples of patient information leaflets currently being distributed. Several comments misunderstood the proposed rule and commented as though FDA was seeking to immediately



establish a mandatory Medication Guide program to provide patient labeling for all prescription drug and biological products.

A. Patient Information--Legal Authority

1. Some comments stated that the proposal regulates the professional practice of pharmacy, which is the purview of the State boards of pharmacy. The comments stated that FDA cannot extend its statutory authority to regulate product labeling to require that pharmacists distribute information about prescription medications that they dispense. One comment added that this initiative would set a precedent for FDA to impose other regulations on individual health care professionals.

Both the proposal and the final rule seek to assure that patients receive information necessary to the safe and effective use of prescription drug products. Federal courts have affirmed FDA's authority to require the dispensing of patient labeling for prescription drugs, and that such requirement does not interfere with the practice of medicine (Pharmaceutical Mfr. Ass'n (PMA) v. FDA, 484 F. Supp. 1179 (D. Del. 1980), aff'd per curiam, 634 F. 2d 106 (3d Cir. 1980)).

In PMA v. FDA, the court stated that "[t]he fact that the practice of medicine is an area traditionally regulated by the states does not invalidate those provisions of the act which may at times impinge on some aspect of a doctor's practice" (Id. at 1188). The court reasoned that the regulation at issue, which required pharmacists and dispensing physicians to distribute patient labeling with prescription drugs containing estrogens,

did not forbid a physician from prescribing a prescription drug product, nor did it limit the physician's exercise of professional judgement (Id.). Moreover, the court stated that the regulation not only did not limit the information that a physician may provide to his or her patients, but rather it fostered open discussions between physicians and patients (Id.). Similarly, this final rule does not inhibit a prescriber or pharmacist from exercising his or her professional judgement, nor does it limit the information that can be given to the patient. The prescriber or pharmacist may add to the information and discuss any aspect of the product with the patient, thereby promoting better communication between health care professionals and their patients.

FDA also does not agree that it lacks statutory authority over written information about prescription drug products that is dispensed by pharmacists. The agency's authority for this final rule was set forth in the proposed rule (60 FR 44182 at 44210). In short, under section 502(a) of the act (21 U.S.C. 352), a drug product is misbranded if its labeling is false or misleading in any particular. Further, under section 505(d) and (e) of the act (21 U.S.C. 355(d) and (e)), FDA must refuse to approve an application and may withdraw the approval of an application if the labeling for the drug is false or misleading in any particular.

Section 201(n) of the act (21 U.S.C. 321) describes the concept of "misleading" and specifically provides that in

determining whether the labeling of a drug is misleading, there shall be taken into account not only representations or suggestions made in the labeling, but also the extent to which the labeling:

[f]ails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the [drug] * * * under the conditions of use prescribed in the labeling * * * or under such conditions of use as are customary or usual.

These provisions, along with section 701(a) of the act (21 U.S.C. 371), authorize FDA to issue regulations designed to ensure that patients using prescription drug products receive information that is material with respect to the consequences which may result from the use of these products under labeled conditions. The proposed rule also described the agency's authority for requiring Medication Guides for generic drugs and biological products.

The act authorizes FDA to regulate the marketing of drug products so that they are safe and effective for their intended uses and are properly labeled. As previously stated, FDA has determined that written patient labeling containing information on warnings, precautions, contraindications, side effects, directions for use, and other information is necessary for the

safe and effective use of prescription drug products of "serious and significant concern."

2. Several comments contended that FDA lacks the legal authority to request (or require) patient labeling for prescription drug products. One comment cited section 503(b)(2) of the act (21 U.S.C. 353), which expressly exempts prescription medications from the requirement for "adequate directions for use."

FDA does not agree with these comments. As previously discussed in response to comment number 1 of this document, the agency's authority to require patient labeling for prescription drugs has been upheld by the courts (PMA v. FDA, 484 F. Supp. 1179 (D. Del. 1980), aff'd per curiam, 634 F. 2d 106 (3d Cir. 1980)).

Section 503(b)(2) of the act exempts dispensed prescription drugs from the "adequate directions for use" requirements under section 502(f) of the act, but does not prohibit FDA from imposing a requirement under section 502(a) that pharmacists dispense labeling directed to the patient that is intended to promote the safe and effective use of these products. In fact, section 503(b)(2) of the act specifically makes labeling dispensed by pharmacists subject to section 502(a) of the act. Section 503(b)(2) of the act was intended to clarify certain statutory requirements of the 1938 act related to the dispensing of prescription drug products. Section 503(b)(2) of the act was not directed toward limiting the Government's authority to

require that pharmacists dispense labeling specifically directed to patients. This interpretation of the act was upheld in PMA v. FDA at 1185-1186.

3. One comment contended that FDA is proposing to create a new subcategory of prescription drugs--those that pose a "serious and significant public health concern"--and that it lacks statutory authority to do so. The comment contended that the act does not grant FDA the authority to instruct manufacturers after approval of what the contents of their labeling must be.

FDA does not agree that it is creating a new subcategory of prescription drugs. The final rule will merely require that those prescription drugs deemed to pose a serious and significant public health concern be dispensed with patient information to ensure they are used safely and effectively.

Under section 502(a) of the act, a product is misbranded if its labeling is false or misleading in any particular. Section 201(n) of the act provides that labeling may be misleading if it fails to reveal facts that are material with respect to the consequences which may result from the use of the product under customary or usual conditions of use. In addition, under section 505(e) of the act, FDA may withdraw the approval of an application if, on the basis of new information, the labeling for the drug is false or misleading in any particular and was not corrected by the applicant within a reasonable time after written notice from the agency.

Accordingly, manufacturers have a continuing obligation to assure that their drugs' labeling is not false or misleading.

Thus, if FDA determines that information about the use of a product should be included in the labeling to prevent the product from being misbranded, it is irrelevant whether FDA makes that determination before or after approval. Oftentimes, after an approved product gains widespread use in the general population, adverse events or other consequences regarding the use of the product are discovered. If the agency were not permitted to revise required labeling based on the product's market experience, its ability to protect the public health would be seriously undermined.

4. One comment noted that FDA has authority to determine that the product as labeled is unsafe or ineffective based on information before the agency, and if it so determines, it may withdraw approval, under section 505(e) of the act. In the case of this rule, the comment stated that FDA has not articulated what procedures it expects to follow to make the determination under section 505(e) of the act.

If such a case arises, FDA will use the procedures set forth in the act and the Public Health Service Act, and their implementing regulations.

5. Several comments stated that FDA has the authority to establish a mandatory patient labeling program only after notice and comment rulemaking on a drug-by-drug basis, and that one regulation requiring patient labeling for all products denies manufacturers due process.

It is well settled that the act authorizes FDA to require patient labeling for prescription drugs (PMA v. FDA, 484 F. Supp. 1179 (D. Del. 1980), aff'd per curiam, 634 F. 2d 106 (3d Cir. 1980); "Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Bill, 1997," S. Rept. 104-317, 104th Cong., 2d sess., p. 132, July 11, 1996). FDA does not believe that the Medication Guide rulemaking raises any due process issues. First, FDA provided notice and opportunity for public comment on the proposed program. Second, unlike the proposal, the final rule only applies to prescription products that pose a serious and significant public health concern requiring distribution of necessary patient information. In terms of the specific information required in Medication Guides, sponsors will have an opportunity to discuss the specific content with the agency, to request an exemption or deferral of certain Medication Guide requirements (see § 208.26(a)), and to appeal an agency decision if the sponsor disagrees. (See 21 CFR part 10, Administrative Practices and Procedures.) Third, the agency has set forth the circumstances in which it will determine which products pose a serious and significant public health concern requiring distribution of written patient information (see § 208.1(c)). This decision may be challenged as well.

Although FDA used notice and comment rulemaking to require patient package inserts for certain prescription drug products in the 1960's and 1970's, this proved to be overly cumbersome and impractical. The agency notes that in the 1980's and 1990's, the

vast majority of patient package inserts were instituted on a voluntary basis by the sponsor or incorporated as part of the approved product labeling at the time of initial approval of the product. FDA did not engage in notice and comment rulemaking for any of these patient package inserts.

Furthermore, the agency notes that individual notice and comment rulemaking is not required for changes to the labeling of FDA-regulated products. FDA has the statutory authority to regulate prescription product labeling, while holders of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and product license applications (PLA's) have the continuing obligation to ensure that their products' labeling does not cause the product to be misbranded.

Moreover, general patient medication information requirements need not be based on a drug-by-drug identification of specific hazards. Rather, general requirements are amply justified by the data presented in the 1995 proposed rule demonstrating that there is substantial noncompliance by patients with drug therapy, that providing patients with information about drugs increases the degree to which they use them properly, and that existing drug-dispensing mechanisms are not adequately providing the information to patients.

6. Some comments contended that the provision of patient labeling would adversely affect the legal liability of manufacturers, physicians, pharmacists, and other prescribers or dispensers of prescription drug products by abrogating the

"learned intermediary doctrine." Some comments urged that FDA provide for Federal preemption of State regulation with respect to civil tort liability claims and other labeling requirements. The comments claimed that without preemption, FDA regulation would encourage "failure to warn" claims and challenges to the adequacy of the patient labeling, especially compared to professional labeling.

Tort liability can not be a major consideration for FDA which must be guided by the basic principles and requirements of the act in its regulatory activities. Nevertheless, FDA does not believe that this rule would adversely affect civil tort liability for several reasons. First, tort liability depends on a number of factors surrounding the manufacture, distribution, sale, and use of a product, and the nature of the injury, and not just on the information provided or not provided to patients. Second, the agency believes that providing patients with written information about the proper use of prescription drug products of "serious and significant concern" could reduce potential liability by improving patient compliance and patient monitoring of serious adverse events, thus decreasing drug-induced injuries and hospitalizations. Written information could also represent a clear opportunity for patients to be made aware that certain risks accompany drug therapies, and that not all serious adverse events are caused by deficiencies in the drug product or actions of the health professional. Third, the written patient medication information provided does not alter the duty, or set

the standard of care for manufacturers, physicians, pharmacists, and other dispensers. Fourth, no evidence has been presented that patient labeling currently required by FDA regulation has caused a noticeable change in tort rules affecting civil liability. The courts have not recognized an exception to the "learned intermediary" defense in situations where FDA has required patient labeling, and the courts seem increasingly reluctant to recognize new exceptions to this defense.

FDA believes that the information required under these regulations is necessary for patients to safely and effectively use prescription drug products that have been determined to be of "serious and significant concern." In most cases, the information required by FDA will be such that States will have little reason to impose additional labeling requirements. Additionally, Federal preemption could unduly interfere with the goals and objectives of existing State programs imposed under the Omnibus Budget Reconciliation Act (OBRA) of 1990, which requires that pharmacists offer to counsel Medicaid patients about their prescription drugs. Many States have extended this requirement to all patients who receive prescription drugs, and some States have required that patients receive written medication information. This final rule is intended to complement these State efforts, not replace or hinder them.

FDA does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations. FDA's regulations establish the minimal standards necessary, but were not intended to preclude

the states from imposing additional labeling requirements. States may authorize additional labeling but they cannot reduce, alter, or eliminate FDA-required labeling.

To reduce liability concerns brought about by the perception that medication information must be tailored to each individual patient, the final rule has been changed to eliminate references to individual patients. FDA believes that Medication Guides for products of "serious and significant concern" should provide important and specific risk and benefit information that is applicable generally to the largest number of patients. Health care professionals bear the primary responsibility for informing individuals about patient-specific benefits, risks, and directions for using prescription medication.

7. Some comments stated that manufacturers should be responsible only for providing medical and scientific information about their products to health care professionals. Several comments stated that the health care provider is in the best position to supply personalized information because the manufacturer's advertising, medical, or legal departments cannot possibly craft patient-specific information.

As previously indicated, FDA agrees that health care providers who directly communicate with patients are in the best position to educate patients by personalizing oral and written information. However, FDA does not agree that manufacturers should not be responsible for informing patients about their products when circumstances make this important. Thus, manufacturers have been required to provide patients with

information about certain products, such as oral contraceptives. Likewise, the final regulations will require that manufacturers develop and disseminate patient information only for selected medications that the agency has determined cannot be used safely and effectively without patient information.

8. Some comments stated that Executive Order 12866 permits FDA to issue only such regulations as are "necessary by compelling public need, such as material failures of private markets to protect or improve the health and safety of the public." Noting FDA's assertion that numerous sources of prescription medication information suitable for distribution to patients have been developed, the comments concluded that the regulation would violate Executive Order 12866.

FDA believes that the final rule is in compliance with Executive Order 12866. To date, the private sector has not succeeded in providing prescription medication information to a large portion of Americans. Section 601 of the Appropriations Act will provide the private sector with sufficient time to meet the legislation's goal of distributing high quality information to a large number of consumers. These goals permit significant variability in the content of patient information. This final regulation applies only to a small number of products that are of "serious and significant concern." Therefore, these regulations are consistent with section 1(b)(8) of Executive Order 12866, which states that "Each agency shall identify and assess alternative forms of regulation and shall, to the extent

feasible, specify performance objectives, rather than specifying the behavior or manner of compliance that regulated entities must adopt" (58 FR 51735, October 4, 1993). The final rule requires the development of Medication Guides only for those few medications where the need for patient information is critical to proper use of the drugs. In those cases, a voluntary system will not suffice because it would not satisfy the "compelling public need" for good patient guidance.

9. One comment insisted that the entire proposed rule and preamble is too vague and as such cannot be commented on in a meaningful manner.

The agency has reviewed both the proposed rule and public comments and has concluded that the proposed rule is sufficiently clear. Moreover, no other comment stated that the proposed rule was either vague or ambiguous. Despite this consensus, FDA has made changes in the final rule to make the program clearer, in particular more specifically defining the circumstances under which a Medication Guide will be required for a drug product.

B. Medication Guide

10. Several comments argued that providing written information is not an effective intervention, citing a number of studies indicating no significant changes in compliance with medication instructions. Other comments stated that FDA makes a number of "unsubstantiated" assumptions regarding the impact of written material on improved interaction with health care professionals, on decreased unnecessary physician visits, and on

improved quality of health care. Some comments argued that FDA erroneously assumes that a direct relationship exists between providing patient information and improved health outcomes.

FDA believes that the research consistently concludes that written information can improve patient knowledge, and that improved patient knowledge about how and when to take medication, and what to expect from taking the medication, contributes to better medication-taking behavior, including regimen adherence. The agency's conclusions are based upon published literature cited in the August 24, 1995, proposal (60 FR 44182 at 44233 through 44235). For example, estimates of hospital admissions caused by preventable adverse drug reactions (ADR's) and noncompliance were based upon a thorough literature review. To achieve the most accurate estimate, FDA relied upon a meta-analysis of this literature and upon additional studies that directly examined the cause of hospitalizations (Ref. 1). Estimates of the number of preventable ADR's, as distinguished from nonpreventable ADR's, were based upon an analysis made by the study's authors.

FDA agrees that health care problems are multifaceted, requiring a number of interventions. FDA maintains, however, that patients' knowledge about their treatments (which is consistently improved by written information) can and will contribute to such improvement. The experience FDA has had with written information (evaluated by Rand and oral contraceptive studies) (Refs. 2 and 3), with voluntarily supplied information

(cited in the proposal in 60 FR 44182 at 44187), and the experiences in other nations with patient package inserts (Ref. 4) demonstrate that patient information does generally contribute to improvements in the parameters measured. Although it is true that FDA's analysis makes certain assumptions, the agency believes that they are valid. For example, patients who discuss the utilization of medications in a more informed manner have better quality interactions with a health care professional.

11. Several comments stated that a "one size fits all" mentality will not work because different patients have different needs in acquiring and understanding medication information. In contrast, one comment pointed to research indicating that many groups share preferences for quality information. For example, older and younger adults share preferences regarding how medication information should be organized (which was in a manner similar to the suggested Medication Guide format), and better remember instructions if they are presented in the preferred grouping and order.

The final rule specifies both content and format requirements to ensure that every affected patient receives certain basic information, the content of which is tailored to the individual drug. The modest format requirements are based on the best available research and contain such common sense provisions as a minimum type size generally readable even by older individuals with reduced visual abilities. The content provisions are more extensive and contain every category of

information that might be needed for any drug requiring patient labeling. FDA notes, however, that it does not expect each Medication Guide to contain information in all of the categories specified in § 208.20 because not every category will be relevant to every drug. Rather, the agency expects that a Medication Guide will contain only that information that is necessary for the safe and effective use of the particular drug. In recognizing the need for a certain amount of flexibility in the design and content of Medication Guides, the final rule provides in § 208.26(a) that FDA will consider changes to any Medication Guide requirement, except those contained in § 208.20(a)(2) and (a)(6), on the basis that the requirement is inapplicable, unnecessary, or contrary to patients' best interests. FDA has determined that it would never exempt a Medication Guide from the requirements that it be scientifically accurate and based on the product's approved professional labeling, or that it contain the legend identifying it as a Medication Guide. The agency anticipates exempting Medication Guides from specific content requirements that are shown to be inapplicable, unnecessary, or contrary to patients' best interests. The agency believes that this approach provides sufficient standardization to ensure uniform quality of Medication Guides, while also providing the flexibility to allow each Medication Guide to be tailored to the specific product and its population.

FDA agrees with the comment concerning the value of instructions presented in a preferred grouping and order.

Accordingly, the final rule continues to require the order of presentation of certain specific headings. This was discussed more fully in section II of this document.

12. Some comments stated that medication information could, through suggestion, cause patients to develop the side effects listed, while other comments disagreed with this view. Some comments cited studies (Ref. 5) indicating that patient leaflets would increase patients' anxiety, causing them either not to initiate therapy or to discontinue it. One comment asserted that previous government-mandated patient leaflets have overemphasized risks, leading to decreased compliance.

The effect of receiving written information on patients' propensity to report side effects has been evaluated in several studies (Refs. 6 and 7), most of which have not found an increase in suggestion-induced side effects. For example, in a study by Morris and Kanouse (Ref. 8), patients taking thiazide medication were asked to report any health problems they experienced. The patients who were given a leaflet mentioning side effects were no more likely to report "health problems" following the initiation of the regimen than those who did not receive a leaflet. However, those who received the leaflet were more likely to say that the health problem was caused by the medication. The authors concluded that the leaflet did not cause suggestion-induced side effects, but did increase the attribution of reactions to the action of the medication. It is unclear how many of these side effects attributions were warranted by the

action of the ingested medication or some other factor. However, the authors noted that if leaflets help patients understand the causes of their reactions, patients can better decide how to respond to these reactions.

Although there have been anecdotal reports of increases in anxiety and deterrence in taking medications, FDA is not aware of any studies that document such an effect and therefore disagrees with the comments on this point. An FDA-sponsored study reported by the RAND corporation in 1981 measured the broad-scale impact of a variety of patient leaflets (Ref. 2). The postulated negative effects did not occur. Few patients demonstrated increased anxiety, there was no significant decrease in reported compliance, and few (3 of 2,000) patients returned their medication.

FDA does not agree that patient leaflets already in use have overemphasized risks. These patient leaflets, such as those for oral contraceptives, have been written for medications that pose significant risks to patients. It is essential that the healthy young women who use oral contraceptives be informed that the products can increase the risks of sudden life-threatening outcomes, especially when the risks can be avoided or reduced by the patient (e.g., by not smoking). The agency strives for a balanced description of the benefits and risks of taking the medication in the patient leaflets it approves. To reinforce that balance, the agency has changed § 208.20(b)(3) to allow discussion of the benefits of treatment.

13. Some comments stated that patient information would detrimentally affect patients' relationships with health care providers. These comments variously suggested that patient information would reduce incentives for health care providers to communicate with patients, or would inappropriately increase the number or length of patients' contacts with health care providers because the information could confuse or alarm patients. Other comments stated that FDA did not properly emphasize the importance of the physician in the patient encounter, arguing that physicians should decide if and when the patients should receive a Medication Guide.

FDA agrees that health care providers should be the primary source of information about medications for their patients. The purpose of written information is to reinforce and supplement, not to interfere with, the doctor-patient relationship. This final rule is intended to help ensure that patients receive accurate and easy-to-understand information necessary for the safe and effective use of their medications, and to provide pharmacists, physicians, nurses, and other counselors with information that can supplement oral counseling. As discussed in the proposal (60 FR 44182 at 44188 through 44189), virtually all studies indicate that a combination of written and oral information works better than either of these interventions alone to increase patients' knowledge about their medications.

FDA does not believe that written information will be detrimental to patients' relationships with their health care

providers. Rather, written information should improve this relationship by improving patients' ability to communicate about their medications. Improved education should also increase patients' ability to take care of themselves and to make more knowledgeable inquiries of health professionals. Research indicates that for most patients the information in the patient leaflet for oral contraceptives did not change the length of patients' visits. It did, however, influence the content of the interaction, focusing more of the interaction on the medication (Ref. 3).

FDA's 1992 and 1994 surveys of people initiating prescription medication treatment (Refs. 9, 10, and 11) indicated that the increased use of written patient information did not decrease the amount of orally supplied information.

14. One comment pointed out that labeling changes occur frequently during the life cycle of a product. Thus, distribution of revised Medication Guides resulting from these changes will need to be carefully controlled to ensure that the most up-to-date information is available for dissemination to the patient.

Section 208.20(b)(8)(iv) of the final rule requires that the date of the most recent revision be printed on the Medication Guide so that patients who receive multiple materials can identify the most recent information. FDA does not contemplate that changes in professional labeling would necessarily require changes in patient information. However, if changes in the

professional labeling are significant enough to affect a product's Medication Guide, the manufacturer would be required to make related changes at the same time.

15. Some comments stated that the final rule should not require approval of all written information prior to its use. Instead, they urge that the rule should simply specify topics to be included and require clarity, but that FDA audit, as opposed to preapprove, such information. Similarly, one comment suggested that prior approval should not be required for "minor changes," such as the company name or address.

The final rule requires that FDA approve a Medication Guide prior to distribution to ensure that it is consistent with the package insert and is adequate to help ensure safe and effective product use. Because Medication Guides will be required only for drug products of "serious and significant concern," FDA believes that prior approval of the information necessary to the safe and effective use of the product is especially important. The agency will allow only very minor changes to be made without prior approval and has accordingly revised § 314.70(b)(3)(ii) (21 CFR 314.70(b)(3)(iii)) and § 601.12(f) (21 CFR 601.12(f)) to indicate that. The agency has added the change to § 601.12(f), which was not included in the proposal, to make the requirements for drug and biological products the same.

16. One comment suggested that FDA be held to a 30-day approval time on NDA supplements for patient labeling, and that if 30 days pass without comment by FDA, the patient labeling should be automatically approved.

As discussed previously in this document, Medication Guides would most often be required at the time of product approval. Thus, most Medication Guides would be covered under the timeframes designated under the Prescription Drug User Fee Act (PDUFA) (21 U.S.C. 379).

However, for the rare situations in which Medication Guides are required subsequent to product approval, PDUFA timeframes are not relevant unless new clinical information is submitted in support of the labeling changes. Under these circumstances, FDA will endeavor to approve these changes as quickly as possible.

17. Some comments urged that the regulations require patient labeling to be standardized in format and content, much like food labeling requirements, and be harmonized with international requirements.

Consistent with the views of many consumer groups, FDA agrees that a standard format would be extremely helpful in aiding readers to quickly find information of particular interest. However, the agency was persuaded by the written comments and presentations at the February 1996 public workshop that flexibility should be afforded in the design of Medication Guides. Different medications and patient populations may require somewhat different presentations to ensure that information is effectively communicated.

FDA has determined that the best approach is to retain the standardized format but be flexible enough to allow changes when they are needed to more effectively communicate with a special

population or to permit innovation. The final rule specifies the order of topics, the text of the headings to be used, and the location of required contents within the headings. FDA will consider changes to the format and content if the requirements are inapplicable, unnecessary, or contrary to patients' best interests. In reviewing requests for changes, the agency will be interested in receiving any data regarding more effective design or methods of communication.

FDA believes that Medication Guides are different from the numerical listings of food labels because of the wider variety of issues and more complex meanings covered in a patient leaflet. The greater difficulty of communicating medication information justifies departure from the standard format.

Regulations in Europe standardize the formats of patient leaflets within but not across countries. Therefore, the extent to which U.S. standards for Medication Guide formats would be consistent with evolving format standards being developed through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is unclear at this time.

18. One comment suggested that § 208.1(a) be revised to read that "[t]his part does not apply to prescription drug products administered in an institutional setting (such as hospitals, nursing homes, doctors' and dentists' offices, or other health care facilities such as clinics), or in emergency situations." [Emphasis in original comment.]

FDA does not agree with this comment. Section 208.1(a) states that part 208 applies primarily to medications used on an outpatient basis without direct supervision by a health professional. In addition to the wording change in § 208.1(a) of the final rule that reflects the regulation's focus on providing Medication Guides for all prescriptions for drug products of "serious and significant concern," the agency made the small change of moving the word "primarily" in the second sentence of § 208.1(a) to immediately follow the word "applies." This was done to make it clear that Medication Guides will usually be required for products used on an outpatient basis without the direct assistance of a health care provider.

The agency believes that on rare occasions it may be necessary to require a Medication Guide for a product that is used in a physician's office or other health care facility, and this change reflects the agency's desire for the flexibility to accomplish this. The agency notes that prescribers would not be exempt from providing mandatory Medication Guides if they dispense a product to patients for outpatient use.

19. One comment disagreed with FDA's reasoning as to why the Medication Guide proposal relates to prescription products that are used "primarily on an outpatient basis without direct supervision by a health care professional." The comment asserted that this reasoning is incorrect in that these outpatients are, indeed, under the direct supervision of a physician or pharmacist.

The comment misunderstands FDA's use of the phrase "direct supervision." The agency uses the phrase to describe situations in which a health professional is administering the medication on site, whether it is at a physician's office or at a health facility.

20. One comment stated that FDA should clearly define how it identified, developed, and tested the seven components of "useful" information.

To identify and develop the seven components, FDA relied on several studies it conducted involving various aspects of patient information (Refs. 2, 12, 13, and 14), as well as other published studies (Ref. 15). Additionally, FDA relied on a number of clear writing manuals (Refs. 16, 17, 18, and 19) and legibility guidelines used by the nonprescription drug industry (Ref. 20). FDA also relied on its extensive experience gained over the past two decades developing and approving patient labeling, as well as preliminary advice obtained from the pharmaceutical industry, pharmacy and medical professional organizations, and consumer groups. All of this information and guidance was combined to create the list of seven components. This list was published in the 1995 proposed rule to obtain public comment. Furthermore, the agency held a public workshop in February 1996 to obtain additional comment on the seven components. The agency maintained a public docket for comment until March 6, 1996, to accept comments specific to these seven components (Ref. 9). Based on information and comments received during the workshop

and comment period, the agency made certain changes to the components.

FDA proposed these criteria for identifying and evaluating the quality of the information included in leaflets voluntarily distributed to patients. While the voluntary private-sector program for which the seven components were originally developed is outside the scope of this final rule, the agency believes that these criteria are important and has therefore retained them as requirements for Medication Guides. The broad acceptance of these components has been affirmed by Congress by their inclusion in the Medication Guide language contained in the 1997 Appropriations Act and their use in the voluntary private-sector program.

21. The 1995 proposed rule defined the criterion of scientific accuracy to mean consistency with FDA-approved product labeling, and proposed requiring that Medication Guides include the verbatim statement "Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide." Many comments stated that patients could become confused and experience problems if a product was prescribed for an off-label use or regimen that was not described in their medication information sheet.

The agency does not believe that a change in response to these comments is warranted. The comments did not explain why patients would become confused or elaborate on the problems that might ensue. Moreover, the agency believes that the statement to be included in Medication Guides is sufficiently clear and will

be helpful to patients. If patients have questions about the product's use, this may stimulate profitable discussion with an appropriate health care professional.

22. Several comments stated that FDA's criteria for determining whether a product would be designated as being of "serious and significant concern" and hence that it would be accompanied by a Medication Guide are so broad as to include all pharmaceutical products, providing little or no guidance to manufacturers. Some comments stated that FDA's purpose in requiring 10 drugs or drug classes each year was to eventually require Medication Guides for all prescription drugs.

FDA agrees that the proposed criteria for determining whether products or classes of products must be accompanied by Medication Guides can be more narrowly defined. Although the agency asked for comments on the appropriateness of the criteria, there were no suggestions made for improving them. Therefore, FDA has made several changes of its own in the final rule to clarify the purpose of Medication Guides and to describe more clearly the circumstances in which medications will be determined to be of "serious and significant concern" requiring Medication Guides.

The agency has rewritten § 208.1(b) describing the informational goals of Medication Guides. This section states that the agency must determine that information is "necessary" to patients' safe and effective use of the product. This is a high standard that will be met in only a small number of cases.

To conclude that the information is necessary, the agency must find that one or more of the three circumstances in § 208.1(c) exists. The four cases discussed in the preamble to the proposed rule have been condensed to three circumstances in order to avoid redundancy and to further clarify the circumstances in which FDA will require a Medication Guide. The three circumstances are: (1) The drug product is one for which patient labeling could help prevent serious adverse effects; (2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or to continue to use, the product; or (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. These circumstances describe those situations in which patients must have information to use their medications safely and effectively.

FDA does not expect that these circumstances will be regularly presented and thereby determine that Medication Guides are required for many or most medications. Rather, the agency intends to require patient labeling only if it is needed for the safe use of the product or critical to the effective use of the drug, and expects that this will be infrequent. In reviewing its past recommendations that manufacturers prepare patient labeling for particular products, FDA has determined that it initially overestimated the number of products or product classes per year that would be required to have a Medication Guide. FDA now estimates that on average no more than 5 to 10 products per year

would be determined to be of "serious and significant concern" and would thus require Medication Guides.

The following examples will illustrate in more detail each of the three circumstances in which a Medication Guide will be required:

(1) Where patient labeling could prevent serious adverse effects:

These are cases in which there is a known "risk control strategy" (e.g., recognition of the early warning signs of lactic acidosis, a potentially fatal side effect, during metformin treatment so that the drug can be stopped and a physician contacted immediately) or where easily taken preventive measures can prevent harm, such as using sun block to avoid serious photosensitivity reactions with photofrin, or avoiding a concomitant therapy that can lead to a dangerous accumulation of the drug.

(2) Where there are serious risks (relative to benefits) of which patients should be made aware because the information could affect patients' decisions to use, or continue to use, the drug:

This is a case where the risk of a drug is relatively great, greater than a patient would anticipate given the relatively benign condition being treated (e.g., isotretinoin is used to treat acne, not usually considered a seriously morbid condition, but the drug can cause severe birth defects in an exposed fetus), where understanding the adverse effects is critical to a choice among alternative treatments with different safety and effectiveness profiles (e.g., choice of barrier contraception

versus oral, injectable, or implantable birth control), or where there is an important relation of duration of use to risk (e.g., increased risk of endometrial cancer with chronic administration of oral estrogens, or increased risk of habituation with prolonged use of benzodiazepine hypnotics).

(3) Where the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness:

This is a case where nonadherence could compromise patients' health by interfering with effectiveness; e.g., labeling could remind people that taking alendronate sodium at least one-half hour before the first food, beverage, or medication of the day with plain water only (other beverages, food, and some medications are likely to reduce the absorption of alendronate), is essential to the drug's effectiveness in treating osteoporosis.

Medication Guides would not be required for general admonitions, such as, "Remember to take your antihypertensive medication daily." Rather, Medication Guides would be used to communicate messages specific to the serious risks associated with certain medications.

FDA wishes to note its expectation that the vast majority of Medication Guides will be required when a product is first approved. Consistent with past procedures when recommending that certain products should include FDA-approved patient labeling, FDA intends to notify sponsors by letter, during the product's

review process, that a Medication Guide is required for the product.

In general, FDA does not anticipate determining that currently marketed products are of "serious and significant concern," unless there is a compelling public health need. At this time, the only currently marketed products for which FDA intends to require Medication Guides are products in classes for which FDA has requested that manufacturers supply patient labeling, but where some manufacturers have failed to provide this information (e.g., benzodiazepine hypnotics and nonsedating antihistamines with boxed warnings). FDA believes that patients receiving similar medications, with similar risks, should receive similar approved patient labeling for all products in the specific pharmacologic class. A Medication Guide will also be required when new information becomes available raising a serious safety or efficacy concern about an FDA-approved drug.

Over the years, FDA has approved a number of patient information leaflets. Some of these leaflets concerning a class of drugs (e.g., oral contraceptives, estrogen replacement products) have been required under notice and comment rulemaking. In addition, some manufacturers have supplied, and FDA has approved, patient information leaflets for several other drug products (e.g., isotretinoin, metformin, alendronate sodium, and epoetin alpha).

Manufacturers whose approved labeling already includes patient-directed labeling must continue to distribute such labeling. FDA believes that this information provides a valuable

service to patients that should not be disrupted. In time, FDA intends to review all existing patient labeling to determine whether it is subject to this part. If existing patient labeling is found to meet the circumstances in § 208.1(c), FDA will notify sponsors directly of such determinations and will allow them sufficient time to conform such labeling to the requirements of this final rule.

23. One comment argued that because prescription drug wholesalers have no contact with patients they satisfy the definition of "distributors" under proposed § 208.3. Consequently, the comment suggests that FDA more clearly define the roles of dispensers and distributors.

FDA agrees that drug wholesalers should not be considered dispensers under proposed § 208.3(a), but rather as distributors under § 208.3(d). FDA acknowledges that in several places in the proposal, the term "distributor" was used when, in fact, the term "dispenser" should have been used. These inconsistencies have been corrected in the final rule.

24. A number of comments addressed the relatively large number of Spanish-speaking individuals in the United States and the need for Spanish (and other language) Medication Guides. One comment suggested that existing computer data bases could be adapted easily to translate patient information into foreign languages commonly spoken in the United States. One comment claimed that proposed § 208.20(a), mandating that Medication Guides be in English, is inconsistent with FDA's request for comments on how best to provide information to populations who do

not speak English. One comment stated that FDA should permit verbatim translations of Medication Guides without requiring a submission for approval.

FDA encourages, but the final rule does not require, the dispensing of patient information in foreign languages, in low literacy formats, or in braille for visually impaired consumers. Given the development of technology, translations and Medication Guides in other formats may become easier to distribute. However, FDA believes that most of these populations still could benefit from English language leaflets because, for example, a relative or friend could translate the information.

Section 208.20(a)(1) does not prohibit, in addition to English language leaflets, either the distribution of faithful translations, such as materials in other languages or braille, or materials in simplified texts, or using icons or symbols. FDA continues to believe that a multifaceted communications system would help ensure that all consumers receive meaningful patient information.

FDA believes that due to sometimes subtle differences among languages, including syntax and connotation, translation requires judgment and expertise. While the distribution of translations is encouraged, translations would not satisfy § 208.20(a)(1). Moreover, FDA frequently disagrees with sponsors about the appropriate translation of labeling language. The final rule does not require that translations receive FDA approval, but § 208.20(a)(1) requires, that when they are used, they be distributed along with English language texts.

25. Several comments suggested that § 208.20(b)(1) be modified to permit the established name to be used as the most prominent product name and permit the trade name(s) to be listed secondarily.

Application of § 208.20(a)(7) and (b)(1) of the final rule would permit the established name of the product to be more prominent than the brand or trade name. Implementing section 502(e)(1)(B) of the act, § 208.20(a)(7) of the final rule requires that the established name be printed in type at least one-half the height of that used for any proprietary name. Consequently, the established name can be as large as desired, provided that it is no less than one-half the height of the brand or trade name.

26. Several comments suggested that § 208.20(b)(5)(iv) be modified to include what the patient should do if several doses of the drug are missed or if the patient discontinues the regimen.

No change is necessary to § 208.20(b)(5)(iv) in response to these comments. The provision gives manufacturers the ability to include information on missed doses of a medication of "serious and significant concern." The agency has modified this provision to include the phrase "where there are data to support the advice." This change was made to emphasize that any advice of this type must be based on appropriate data or information.

27. Several comments claimed that the required content of a Medication Guide emphasizes the presentation of risks without similar stress on benefits. Some pointed out, for example, that

one of the prototype Medication Guides in the proposal includes information that overemphasizes the risks associated with the medication.

FDA has long maintained that patients need to receive a fair balance of risk and benefit information. FDA does not object to the presentation of product benefit information if it is supported by scientific evidence and is consistent with approved professional labeling. In fact, the agency has added a new sentence to § 208.20(b)(3) to make it clear that, when appropriate, a discussion of benefits of treatment can be included in a Medication Guide. On the other hand, because some medications have potentially serious effects, FDA believes that it is vitally important for patients to receive a truthful description of products' risks.

While FDA believes that benefit information is often understood, the agency is open to learning more about how to communicate risk and benefit information so that patients receive a fair and balanced picture of their medications, without undue emphasis on either risks or benefits.

28. Several comments urged that FDA avoid class labeling, i.e., providing the same information for various products within a class of drugs. Medication Guides, they argued, should be product-specific, rather than class-specific, to address issues unique to particular products.

FDA has accepted both product-specific and class labeling approaches in its past approval of patient labeling and believes that class labeling can be appropriate for products in narrowly-

defined pharmacologic classes. FDA will review drug product labeling when the agency believes that information can be safely applied to the specific covered product.

29. Several comments suggested that the currently available "imprint system," or other descriptors of color, shape, markings, etc., be incorporated in the patient information to facilitate patients' coordinating their medication with the proper patient information. Other comments noted that these descriptors would be excessive.

FDA encourages systems that ensure that the patient is able to identify the individual products dispensed. However, a single system may be difficult to implement. For example, in large pharmacies, dispensers may be unaware when generic suppliers with a different imprint are switched, necessitating a corresponding change in the patient information. Because of the excessive burden that would be imposed, FDA will not require that imprints or other descriptors be included in patient information.

30. One comment asked that the medicine's expiration date be stamped on the patient information. Another comment suggested that patient information sheets include the pharmacist's or provider's telephone number so that patients will know where to call to get their follow up questions answered.

The medicine's expiration date applies only to products stored in the manufacturer's container. Once the product is removed from the pharmacy's storage conditions, the original expiration date may no longer be valid. Further, many state pharmacy laws require that an expiration date appear on the

medication vial dispensed to the patient. Generally, this date is 1 year from the time of dispensing. FDA will not require that patient information include the medicine's expiration date because it is not possible for the dispenser to know the medication's true expiration date.

FDA encourages pharmacists or providers to include their telephone number in the information they give to patients. Many State Boards of Pharmacy rules require that the label on the medication container include the pharmacy's name, address, and telephone number.

31. A number of comments suggested the use of pictograms or icons in addition to text, especially for patients with limited reading skills.

FDA believes that, while pictograms may be helpful in explaining concepts, and icons helpful in providing graphically pleasing and memorable text, it is not clear that these devices are able to communicate concepts adequately regarding the use of prescription medications without the addition of the textual material. Accordingly, FDA will not require the incorporation of icons or pictograms in Medication Guides. However, the agency believes that icons or pictograms, when used in addition to text, are useful and may permit their incorporation on a case-by-case basis if requested by the manufacturer.

32. The proposal solicited comments on page limits (60 FR 44182 at 44208). One comment noted that it may be difficult to explain technical information in consumer language if the page length is limited, especially because page size and length will

vary with the computer equipment used by the dispenser. Another comment argued that the rule should not specify page dimensions because the amount and type of information will vary from product to product.

FDA agrees that a required page limit could put unnecessary constraints on the communication of important information. However, it is important to note that FDA expects that Medication Guides will include only the information necessary for the safe and effective use of the product and other information required to provide needed context. Medication Guides should not exhaustively detail all information known about the product. FDA is concerned that, if unrestrained, lengthy information could result in unnecessary or even dangerous barriers to the effective communication of important concepts. Therefore, the agency will establish a two-page limit as a goal for the communication of the essential information to be included in Medication Guides. Graphic representations, charts or other material supportive of, or in addition to, the essential information should be placed in an "appendix" located at the end of the leaflet. The agency will consider overall length and the inclusion of supportive material in its evaluation of the understandability and legibility of the Medication Guide.

33. Several comments suggested that § 208.20(a)(4) (§ 208.22(a) of the proposed rule) be modified to require at least 12 point type size, rather than 10 point, as proposed.

FDA acknowledges that many prescription drug users are elderly and may have difficulty discerning words written in small

type sizes. Ten point minimum type is larger than that used in many commonly read materials, e.g., newspapers. FDA notes that legibility is determined by a number of factors other than type size. The 10 point minimum was based on the need to balance legibility concerns and patients' reluctance to read longer materials.

34. A number of comments made suggestions for: (1) Optimal presentation of information for patients (e.g., bulleting, outlines, contrast, typeface, leading); (2) the inclusion of specific types of information (e.g., potential treatment outcomes, managing side effects); and (3) providing greater flexibility in the presentation and language used in patient information.

FDA appreciates the comments and suggestions and believes that the final rule provides an appropriate amount of flexibility. The final rule contains a minimum type size in § 208.20(a)(4) and also requires in § 208.20(a)(5) that the information be legible and clearly presented, and, where appropriate, use boxes, bolding, and other highlighting techniques to emphasize portions of the text. In addition, § 208.20(b) of the final rule contains general content requirements for Medication Guides which the agency has said should be tailored to include only those categories of information relevant to the drug product and the need for the Medication Guide. Furthermore, § 208.26(a) provides that changes from the format (and content) requirements will be considered when the requirements are inapplicable, unnecessary, or contrary

to patients' best interests. These provisions will provide sufficient flexibility in the design of Medication Guides.

35. One comment recommended that the final rule require that patient information accompany all medication samples distributed by health care providers.

Under the final rule, Medication Guides are to be dispensed with all prescriptions of drug products that the agency determines are of "serious and significant concern." Prescription drug samples are dispensed under an oral or written prescription of a licensed practitioner. Accordingly, a Medication Guide must be provided with samples of prescription drug products that FDA determines are of "serious and significant concern."

36. Some comments questioned manufacturer compliance under a variety of conditions, such as when changes are made to the Medication Guide, especially for products that are not in unit-of-use packaging. Others questioned whether the agency would request a recall of Medication Guides if important changes are needed. The comments also questioned how the manufacturer could be held accountable or be allowed to confirm the accuracy of the information if third parties are able to make changes to the Medication Guide. Some comments also asked about what criteria must be met for personalized Medication Guides.

In general, FDA intends that changes in Medication Guides be incorporated into the next printing of labeling. If clinically significant information necessitates a change in a Medication Guide, FDA will ask that manufacturers expedite the next printing

to incorporate the change as rapidly as is reasonably possible. In addition, FDA could request that manufacturers notify health care professionals, such as by sending "Dear Health Professional" letters, and rapidly distribute replacement patient information. FDA would also expect manufacturers to use or adapt whatever systems are already in place for making changes to the professional labeling to make changes to Medication Guides.

In response to the comment on personalized information, written medication information may be customized by individual health care practitioners for individual patients by including, for example, the prescription number, the name, address, and/or telephone number of the authorized dispenser and/or licensed practitioner, the specific dosage regimen prescribed, or by including other patient-specific information on leaflets. This information may precede or follow the required information in the Medication Guide, but in no case should the information be more prominent than, or obscure, any required information. FDA believes that such personalization falls within the practice of medicine and pharmacy. However, this final rule pertains only to Medication Guides for drug products of "serious and significant concern," and the information in them must be approved by the agency before they can be distributed. Thus, third parties cannot make substantive changes to a Medication Guide, except in the limited context of personalizing it. Finally, under § 314.70(b)(3) and § 601.12(f), FDA will permit manufacturers to make only very minor changes to Medication Guides without submission of a labeling supplement.

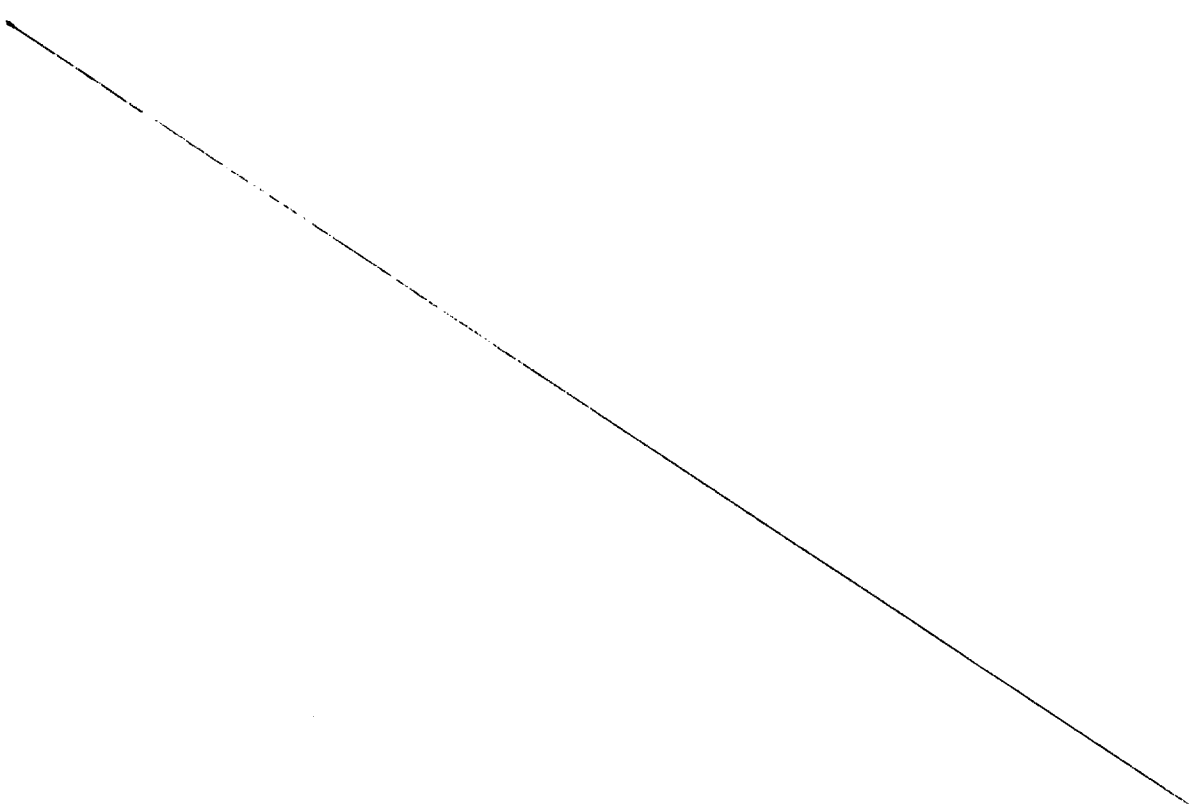
37. One comment stated that the distribution of Medication Guides by drug manufacturers to pharmacies, directly or through drug wholesalers, is not feasible because pharmacies use a variety of operating system platforms and proprietary software. The comment claimed that disks provided by manufacturers or wholesalers may not be compatible with existing systems because, for example, information may be formatted inconsistently with the printing specifications. The comment argued, therefore, that the rule would require that suppliers individualize disks for dispensers, and that such a requirement is overly burdensome.

FDA agrees with the comment that pharmacies use a variety of computer systems. The final rule, in § 208.24(b), however, permits manufacturers and distributors to provide either hard copies of patient information or the "means" for disseminating information. FDA believes that providing manufacturers and distributors with this degree of flexibility will encourage them to develop readily adaptable systems for distributing required Medication Guides. FDA believes that some manufacturers will choose to package certain products in unit-of-use or bulk containers with hard copies of the Medication Guides affixed to the product container. Other manufacturers will work with information system vendors to incorporate Medication Guides into existing pharmacy software systems.

The agency wishes to emphasize that it is ultimately the responsibility of manufacturers to ensure that authorized dispensers receive sufficient numbers of Medication Guides that can, in turn, be dispensed to patients with selected products

that pose a "serious and significant" public health concern. This requirement would not be fulfilled, for example, by a manufacturer providing a pharmacy with Medication Guides in a form that the pharmacy could not use. In cases where unit-of-use packaging or printed copies of Medication Guides attached to bulk packages are not used, the agency feels that market forces will contribute to manufacturers working with the various third-party information providers to ensure that their computerized systems can provide printouts of Medication Guides.

38. One comment argued that the rule would require that manufacturers "provide the dispensers with the means to ensure distribution" of Medication Guides to each patient without adequately defining "the means." The comment asked whether



manufacturers would be required to pay dispensers, provide computer equipment, or develop some other mechanism to ensure that dispensers could distribute Medication Guides. The comment also asked whether manufacturers would be liable for pharmacists' failure to distribute, or distributing the wrong Medication Guide, and whether drug manufacturers have a duty to educate pharmacists about the information contained in the leaflet. Other comments noted that pharmacists currently rely on patient information data bases developed by others, and argued that it would be excessively burdensome to require that pharmacists maintain hard copies of every manufacturer's Medication Guide.

Section 208.24 of the final rule requires that manufacturers provide distributors and authorized dispensers with the means to distribute Medication Guides to patients. To allow for flexibility, FDA did not specify the means, but instead provided examples of effective means, such as providing authorized dispensers with patient information software. As suggested by some comments, FDA believes that most manufacturers will contract with third parties or large pharmacy chains who would develop acceptable dispensing mechanisms that pharmacists could easily incorporate into their practice. The final rule does not specify additional requirements because the agency wants to encourage private-sector innovation.

Section 208.24(e) requires that authorized dispensers provide Medication Guides to patients. A manufacturer has fulfilled its obligation under the final rule by providing those

who dispense its products with Medication Guides in sufficient numbers or the means to produce Medication Guides.

39. Several comments objected to the requirement in proposed § 208.24(c) that patient information be distributed with each unit-of-use package, for both new prescriptions and refills, arguing that manufacturers should be allowed the same options of either providing sufficient paper copies with each shipment, or providing the dispenser with the means to supply Medication Guides without the use of paper, regardless of how the product is packaged.

FDA has accepted the comment's suggestion that the agency exercise greater flexibility in the distribution of patient information for unit-of-use packaged medications. This was not an easy decision and may be reconsidered if alternatives do not succeed in regularly providing patients with the needed information. A unit-of-use package with enclosed patient information guarantees that patients receive the information. No alternative system does so. Although unit-of-use packaging is not the usual packaging in the United States, it is the standard in Europe and thus familiar to any sponsors with international experience.

Proposed § 208.24(c), which would have required the distribution of Medication Guides with each unit-of-use package intended for distribution to patients, has been deleted. This deletion will permit manufacturers the same options for distributing Medication Guides for unit-of-use and bulk dispensed medications. However, to ensure that authorized dispensers know

which unit-of-use packaged products contain Medication Guides (so dispensers will know whether or not to dispense a separate Medication Guide), the term "large volume" as a modifier of the term "container" has been deleted every place it appeared in § 208.24. In addition, the agency has made changes to § 208.24(d) to require that the label of each container of drug product for which a Medication Guide is required instruct the authorized dispenser to provide a Medication Guide and tell the dispenser how the Medication Guide is provided. Because this information is so important, the agency has also added the requirement that these statements appear on the label in a prominent and conspicuous manner.

40. One comment noted that proposed § 208.24(f) specifically exempts authorized dispensers who print Medication Guides from the establishment registration and drug listing requirements of section 510 of the act. The comment contended that this exemption should also apply to prescription drug wholesalers who have never been required to register and list their products with FDA.

Section 510 of the act requires any person (including prescription drug wholesalers), unless exempt by statute (section 510(g)) or by regulation (21 CFR 207.10), who, among other things, changes the container, wrapper, or labeling of any drug product in furtherance of its distribution to register with the agency, as well as to list the product with the agency. FDA does not believe that section 510 of the act would apply to wholesalers who serve merely to pass on Medication Guides from

manufacturers to authorized dispensers. On the other hand, if drug wholesalers make changes to the content of a Medication Guide, just as if they had made changes to the content of the professional labeling, they would be required to register and list their products with FDA.

41. One comment suggested that proposed § 208.26(b), which permitted physicians and pharmacists to withhold a Medication Guide from a patient, be amended to permit the withholding of Medication Guides only if the information "would harm the patient or interfere with the course of treatment." The comment also suggested that the rule require that the prescriber note the reason for withholding the Medication Guide in the patient's record, and that only physicians, not pharmacists, should determine whether Medication Guides should be withheld.

The agency agrees with this comment in part. Section 208.26(b) has been changed to permit only the licensed practitioner who prescribes a drug to direct that a Medication Guide be withheld if it is not in the patient's best interest because of significant concerns about the effect of the information on the patient. Authorized dispensers who are not licensed practitioners may not withhold a Medication Guide. If the patient requests information about a prescription drug subject to this final rule, however, § 208.26(b) requires that the dispenser provide one, regardless of the licensed practitioner's concern. Licensed practitioners may include, depending on the jurisdiction, pharmacists, nurses, physician assistants, and other health professionals, as well as

physicians. Any of these practitioners who have prescribing authority may direct that a Medication Guide be withheld. FDA does not believe that practitioners should be required to document the reason for directing that a Medication Guide be withheld when such decision is deemed to be in a patient's best interest.

FDA believes that it is appropriate to limit this authority because Medication Guides required under this final rule will contain information of crucial importance for the safe and effective use of the product. The agency expects that licensed practitioners will direct that Medication Guides be withheld relatively rarely, and that the decision will be based on special individual circumstances or characteristics of their patients.

42. Several comments stated that the proposed regulations substitute the agency's judgment for that of the health care professional regarding the information individual patients need. Some comments argued that practitioners should decide if and when a patient should receive a Medication Guide, or relevant part(s) thereof. The comments maintain that the rule interferes with the practice of medicine by requiring that Medication Guides be distributed to all patients, even when a health care professional has determined that an individual patient should not receive such information.

The final rule is limited to requiring Medication Guides for products FDA determines present health care concerns so significant that patients must have written information about the products. Medication Guides under this rule will contain

information necessary to patients' safe and effective use of the products. FDA does not believe that providing such information interferes with the practice of medicine. The final rule does not limit the information that health care providers may impart to patients concerning prescribed medications. If physicians disagree with specific aspects of the patient labeling supplied by the manufacturer, they are free to discuss the matter fully with patients, noting their concerns and views. FDA believes the final rule encourages patients to engage in this kind of open discussion with their health care provider. Also, as noted above, the final rule permits a licensed practitioner to instruct that a Medication Guide be withheld from an individual patient if the practitioner believes that it would not be in the patient's best interest to receive the information. Only the patient can overrule this instruction by specifically requesting the Medication Guide.

43. One comment suggested that the final rule exempt only those medications administered under emergency conditions. Another comment suggested that while the distribution of Medication Guides in emergency situations would be impractical, a good faith effort should be made by health care professionals to assure that the patient receives a copy as soon as practicable. In the case of hospitals, one comment advocated that Medication Guides be given to patients upon discharge, if not before. Others argued that Medication Guides should be given to institutionalized patients or their designees, including those in hospitals, long-term care facilities, and prisons. Still others

stated that Medication Guides should be made available in physicians' offices.

FDA has determined that routinely distributing Medication Guides to institutionalized patients is unnecessary because medications dispensed in such facilities are usually administered directly by health care professionals who are readily available to answer patients' questions about their medications. FDA encourages health care institutions to make copies of Medication Guides available to patients who request them, and to maintain compilations of Medication Guides at convenient locations so that interested patients have access to them. However, where the agency determines that the circumstances or characteristics of a particular drug make it necessary, FDA will require the distribution of a Medication Guide to institutionalized patients.

FDA believes that distribution requirements should be sufficiently flexible to permit licensed practitioners to instruct that a Medication Guide be withheld when the information is deemed inappropriate for an individual patient. However, FDA emphasizes that Medication Guides cannot be withheld from patients who request them.

C. Economic/Environmental Issues

44. Several comments stated that FDA's estimated cost for developing patient information was flawed. One comment stated that a particular drug manufacturer took 16 person-months of effort (eight professionals, full-time for 2 months) to develop the patient information for Proscar® and that FDA should rely on

this estimate for the effort needed to produce a new Medication Guide.

FDA agrees that drug manufacturers' recent experiences provide the best source of information for estimating the average cost of developing a new Medication Guide. Indeed, FDA used this sort of information in its Regulatory Impact Assessment, which relied on the July 1993 issue of Pharmaceutical Executive (Ref. 21), in which Merck Pharmaceuticals' manager of information services states that "[d]evelopment of the PPI was a 6-month process, including initial drafting, research to ensure that potential users of Proscar® understood the important information about the medicine contained in the PPI, and revision and refinement based on the results of our research." The article further explains that Merck elected to conduct readability and comprehensibility studies during the development phase.

FDA would not require manufacturers to conduct this level of evaluation prior to issuing a new Medication Guide. Medication Guides are designed to draw upon readily available professional labeling. Even patient labeling drafted at the time of initial drug approval would be based upon the professional labeling, often, FDA assumes, utilizing the same staff that developed the professional label. FDA believes that minimal additional staff, such as a medical writer skilled in writing for laypersons, would be needed; therefore, most of the staff who would work on Medication Guides would be extremely familiar with the medication and its professional labeling. FDA considers 6 months to be an upper bound estimate for developing an original Medication Guide

because Merck conducted testing beyond that required to develop the patient information for Proscar®.

45. Several industry comments claimed that FDA underestimated, perhaps by as much as 30 percent, the annual compensation for nonproduction staff.

FDA believes that the estimated \$70,000 salary used in its analysis is a fair estimation and may even overstate the average salary. According to the Bureau of Labor Statistics Monthly Report of Earnings, nonproduction workers in the Pharmaceutical Preparations Industry (SIC 2834) earned an average of \$49,579 in 1992. The U.S. Bureau of Economic Analysis (BEA), National Income and Product Reports, reported that the ratio of total compensation to wages within this industry is 1.249, resulting in total average 1992 compensation for a nonproduction employee in the pharmaceutical industry of \$61,924. The BEA also reported that the average increase in compensation between 1992 and 1994 was 6.3 percent. Thus, the average total compensation for a nonproduction employee in the pharmaceutical industry in 1994 was \$65,825. FDA has used \$70,000 as a reasonable estimate of this compensation.

46. Several comments stated that FDA should prepare and publish an environmental impact statement (EIS) regarding the effects of the proposed rule, given the agency estimate that the average pharmacy will use 28,600 pages of computer paper and 23 dot matrix printer ribbons annually, and that the agency assumes a total of 71,386 pharmacy outlets use 2,041,688,200 pages of computer paper and discarded 1,641,901 printer ribbons annually.

FDA does not agree that it should develop either an environmental assessment (EA) or an EIS for this rule. This comment relied on environmental impact figures that were based on the effects of a voluntary program of disseminating written patient information concerning all prescription drugs from the proposed rule. The final rule has a much narrower focus because it applies only to a small number of products of "serious and significant concern" and therefore is not dependant on the outcomes achieved by a voluntary program. Thus, these figures are not accurate for this program. Further, 21 CFR 25.24(a)(11) provides a categorical exclusion from the preparation of an EA for actions that establish by regulation labeling requirements for marketing articles if there is no increase in the existing levels of use or change in the intended uses of the product or its substitutes. The requirement for mandatory Medication Guides for medications of "serious and significant concern" will not produce such change because about as many products (on average no more than 5 to 10 per year) will be affected as are currently affected by agency requests that their manufacturers voluntarily produce patient labeling for the products to ensure safe and effective use.

47. One comment noted that the proposal's analysis under the Paperwork Reduction Act demonstrates the large amount of paperwork to implement this program but does not count the cost to produce this paperwork.

FDA did include such costs in its economic evaluation. The Paperwork Reduction Act requires FDA to estimate the costs, in

terms of hours, of reporting and recordkeeping resulting from Government regulations. This estimate was included in the proposal in a table included in section XIV (60 FR 44182 at 44233). The analysis of impacts in the proposal (60 FR 44182 at 44210 through 44213) presented monetary costs of implementing a comprehensive mandatory program, if it were to be instituted. This estimate included a variety of recordkeeping functions, e.g., cost of printing and dispensing Medication Guides and development costs incurred by manufacturers. Further, given the narrowed focus of the final rule, the costs of the paperwork burden, as well as other costs, will be low because only a small number of Medication Guides will be required. However, in recalculating these costs for consistency with the final rule, FDA included manufacturers' resources needed to produce and obtain approval for Medication Guide revisions.

IV. Analysis of Impacts

FDA has examined the impact of the final rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601-612) and under the Unfunded Mandates Reform Act (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages, distributive impacts, and equity).

Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. The Unfunded Mandates Reform Act requires (in section 202) that agencies prepare an assessment of anticipated costs and benefits before proposing any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation).

The agency has reviewed this final rule and has determined that the rule is consistent with the principles set forth in the Executive Order and in these two statutes. Further, the agency finds that the rule will not have a significant effect on a substantial number of small entities, and that it imposes no unfunded mandates to State, local or tribal governments. Indeed, as explained below, the expected annual incremental costs of this rule will not require expenditures significantly above what would be likely to occur in the absence of regulation.

The final rule articulates the agency's decision to require mandatory Medication Guides for those prescription drug products identified as posing a "serious and significant concern." Only when information is critical to patients' safety will a manufacturer be required to distribute this information. In its absence, patients would be more likely to fail to adhere to therapeutically critical directions or to recognize signs and symptoms of both preventable and unpreventable adverse reactions.

Such improper use of prescription medications can increase morbidity and mortality by contributing to additional or prolonged illness. As current estimates of the annual direct medical costs related to the improper use of prescribed medications exceed \$20 billion, even small reductions in the incidence of such events would yield significant savings.

Currently, patient labeling for most high risk products is developed voluntarily by manufacturers on a case-by-case basis. No formal mechanism exists, however, to ensure that all exposed patients receive concise, understandable information, or that the information they do receive is best for consumer protection.

As described previously, FDA currently works with industry on a product-by-product basis to develop patient information sheets for the small number of products that pose the most serious public health risks. The agency does not expect this rule to significantly increase the frequency of this practice, nor will any additional information typically be required because the determining criteria will not change. Nevertheless, the voluntary nature of the current process may result in occasional disagreements between the agency and manufacturers of drug products with "serious and significant concerns." These disagreements and negotiations would delay or preclude patients receiving necessary information. On average, therefore, based on past practice, FDA estimates that, each year, no more than 5 to 10 products with "serious and significant concerns" would develop patient information sheets. Only one of these products, however, would not have developed these sheets voluntarily. Thus only one

additional product with a "serious and significant concern" may have to develop a Medication Guide as a result of this rule. In FDA's view, the nature and magnitude of the adverse outcomes that may result from the misuse of even this one additional product of "serious and significant concern" warrants the implementation of a limited, clearly articulated regulation.

The existence of regulations that mandate the inclusion of critical patient information in a standardized format will ensure that all patients who use drug products with "serious and significant concerns" receive adequate information on their medication. For example, the identification of certain products with "Medication Guide" information will increase patients' ability to recognize products of "serious and significant concern" that require their thorough and careful monitoring. Further, the communication of critical information concerning serious risks and directions for use will improve consumers' ability to identify and to learn essential prescription drug information. In addition, while approximately 70 percent of all patients have reported receiving patient information, this rule will ensure that all affected patients receive these Medication Guides.

Second, by identifying the criteria, format, contents, and other requirements of patient information, manufacturers will be aware of the need for Medication Guides for products under development. Thus, this rule will increase the sponsors' ability to work in conjunction with FDA to develop this information as part of the traditional review package, facilitating FDA's timely

review of the information and helping to assure that drug approvals are not delayed. In the absence of this rule, the ad hoc practice of developing patient information would continue in its currently less efficient and more burdensome form.

Because FDA and industry currently work to assure the development and distribution of this patient information, and because these activities would continue even in the absence of this rule, the rule will impose minimal incremental costs on the industry. Almost every year, several firms are asked by FDA to develop patient information leaflets, and there is no reason to believe that this total number would change substantially. Consequently, as noted above, the agency estimates that one additional product each year will be required to develop information as a direct result of this rule. FDA has estimated a cost of under \$12,000 (or 2-resource months) to develop a patient information sheet for a new drug product. Thus, this incremental compliance cost to manufacturers would be about \$12,000 per year.

Similarly, the distribution of information for the affected products will continue in the same manner. About half of these products (such as oral contraceptives) may be distributed in unit-of-use packaging that contains patient information sheets. These information sheets may cost manufacturers about an additional 2 cents per package for printing and paper. Alternatively, patient information for those products designated as posing a "serious and significant concern," but not marketed in unit-of-use packaging, are distributed through a variety of information channels, including individual leaflets that

circulate with the products, or automated systems that print individual leaflets from larger data bases. Most retail pharmacies, regardless of size, already distribute this information to consumers. FDA anticipates that these activities will continue, as the rule does not dictate any particular distribution approach, but places the ultimate responsibility for ensuring the content and availability of patient information with the manufacturer of the drug product. Moreover, the issuance of this rule will encourage third-party electronic information vendors to incorporate this mandatory patient information into their systems.

According to FDA estimates, approximately 70 percent of all pharmacies supply patient information with prescriptions. The remaining 30 percent will be required to provide medication guides for all drug products with "serious and significant concerns." No more than 5 to 10 such products are expected each year. FDA estimates that each affected drug product may account for 100,000 annual prescriptions, each Medication Guide will consist of one printed page, 50 percent of the affected products are manufactured in unit-of-use packages, and 5 seconds of pharmacist time is necessary to dispense each guide. Based on these assumptions, within 10 years, the total cost for all pharmacies to include Medication Guides for the 50 to 100 identified drugs equals \$434,000 to \$868,000 (about 9 cents per prescription dispensed). The incremental cost of providing these Medication Guides (accounting for the 70 percent current

compliance) would be about 30 percent of this amount, or \$130,000 to \$260,000 per year.

In sum, the actions described in this regulation will formalize the agency's current policy and impose few incremental costs on the affected industry sectors. Public health will be enhanced by ensuring the wider availability of consistent and understandable patient information for products of "serious and significant concern."

With respect to the Regulatory Flexibility Act, even if a few additional products would require patient information sheets, the costs described above would not impose a significant effect on any entity. Thus, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The title, description, and respondent description of the collection of information are shown below with an estimate of the annual reporting burden. Included in the estimate is the time

for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Prescription Drug Product Labeling; Medication Guide Requirements

Description: This final rule imposes reporting requirements on manufacturers of drug products that pose a serious and significant public health concern. These manufacturers will be

required to develop Medication Guides for such products and submit them to FDA for approval.

FDA estimates that on average no more than 5 to 10 products annually would fall under the "serious and significant concern" classification and thus require mandatory Medication Guides. FDA believes that four of these products (estimating conservatively) would be newly approved. One already-marketed product would require a Medication Guide, with two "supplementary" Medication Guides needed for products in the same narrow therapeutic class, and one Medication Guide needed for a generic product in this class. FDA's regulatory impact analysis estimated that applicants would need approximately 2 months of full-time effort (320 hours) to develop for submission to FDA a "model" Medication Guide that would be consistent with the requirements in § 208.20. (A "model" Medication Guide is for a medication in a class that has no previous Medication Guide.) "Supplementary" Medication Guides would require approximately half that time (160 hours), and generic Medication Guides would require 1/20th of the time (16 hours). FDA also estimates that one "serious and significant" Medication Guide sponsor annually may wish to request an exemption or deferral from specific Medication Guide requirements and that this would take approximately 4 hours.

In addition, FDA estimates that two existing Medication Guides annually might require minor changes under § 314.70(b)(3)(ii) or § 601.12(f), necessitating 3 days (24 hours) of full-time effort.

Under § 208.24(e), authorized dispensers are required to provide a Medication Guide directly to the patient (or the patient's agent) upon dispensing a product for which a Medication Guide is required. Thus, the final rule imposes a third-party reporting burden on authorized dispensers, who, for the most part, will be pharmacists. FDA estimates that, over the next 3 years, assuming that 5 Medication Guides are required annually, an average of 10 Medication Guides annually would be available for prescribing and dispensing. Assuming a base of approximately 100,000 prescriptions dispensed for each of these products annually, and subtracting from this base the approximately 50 percent of products with Medication Guides that are dispensed in unit-of-use packages, results in a total of 500,000 prescriptions annually for products that pose a "serious and significant public health concern." Based on data collected in 1996, the agency estimates that at least 70 percent of patients are already receiving some kind of patient medication information voluntarily provided by pharmacists when they dispense prescriptions. Therefore, this final rule would represent an incremental burden, in terms of third party reporting, for only 30 percent, or about 150,000, of these prescriptions. Given 60,574 pharmacies, including chains, independents, and food/drug combinations, this represents an average of 2.5 prescriptions per store, per year. Because FDA estimates that, on average, it would take a pharmacist approximately 5 seconds (.0014 hour) to provide a

Medication Guide to a patient, the overall annual third party reporting burden for this final rule is approximately 212 hours.

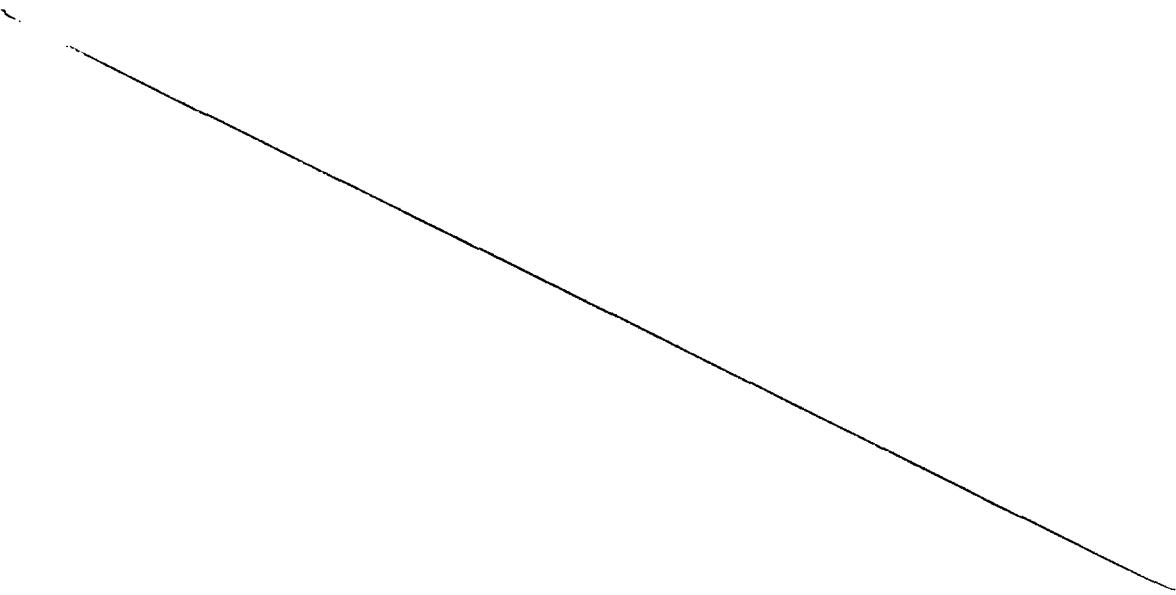
No estimate for recordkeeping burden is necessary because the recordkeeping provision in the proposed rule (proposed § 208.26(c)) has been eliminated and this final rule contains no other recordkeeping provisions.

Description of Respondents: Businesses or other for-profit organizations.

Although the August 24, 1995, proposed rule (60 FR 44182) provided a 90-day comment period under the Paperwork Reduction Act of 1980, and this final rule incorporates the comments received, as required by 44 U.S.C. section 3507(d), FDA is providing an additional opportunity for public comment under the Paperwork Reduction Act of 1995, which applies to this final rule and became effective after the expiration of the comment period. Therefore, FDA now invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

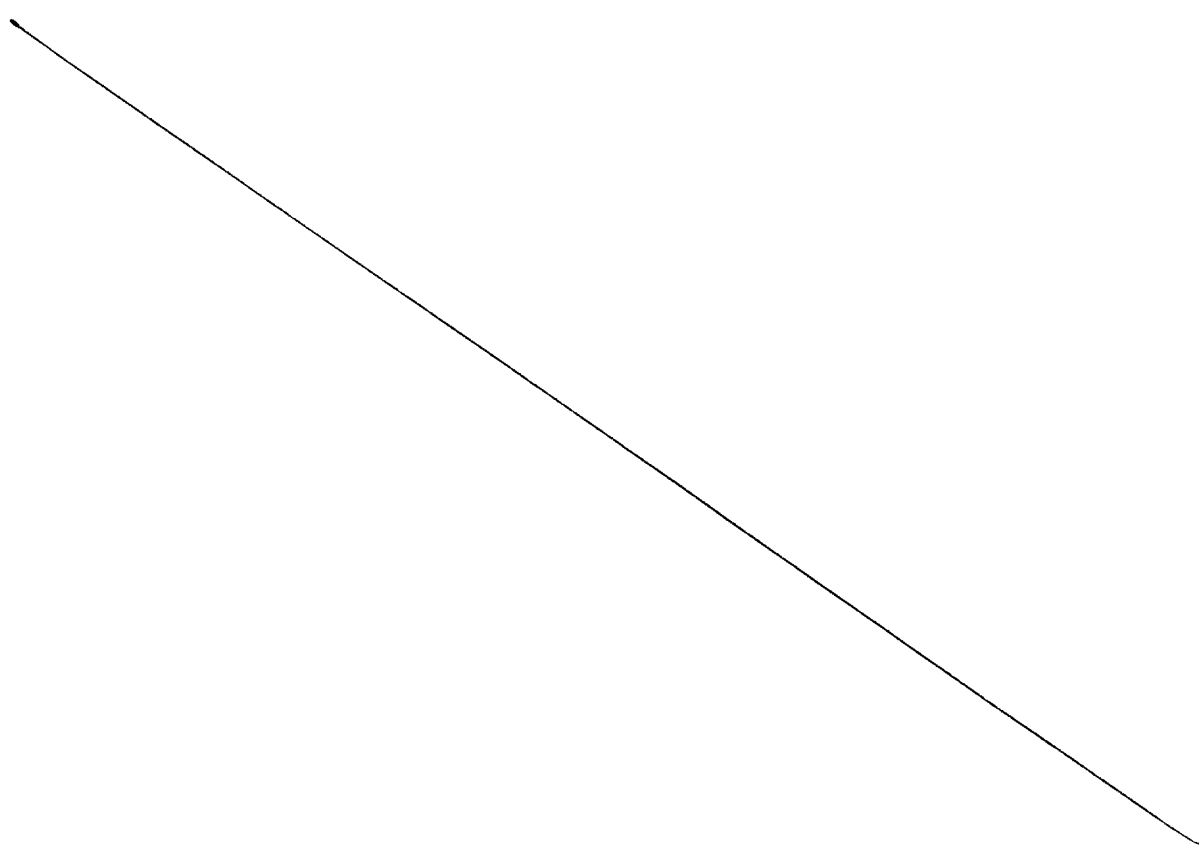
Individuals and organizations may submit comments on the information collection provisions of this final rule by (insert date 60 days from the date of publication in the FEDERAL REGISTER). Comments should be directed to the Dockets Management Branch (address above).

At the close of the 60-day comment period, FDA will review the comments received, revise the information collection provisions as necessary, and submit these provisions to OMB for review. FDA will publish a notice in the FEDERAL REGISTER when the information collection provisions are submitted to OMB, and an opportunity for public comment to OMB will be provided at that time. Prior to the effective date of this final rule, FDA will publish a notice in the FEDERAL REGISTER of OMB's decision to approve, modify, or disapprove the information collection provisions. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



Estimated Annual Reporting Burden ¹					
21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
208.20	8	1	8	242	1,936
314.70(b)(3)(ii) or 601.12(f)	2	1	2	24	48
208.24(e)	60,574	2.5	150,000	.0014	212
208.26(a)	1	1	1	4	4
Total					2,200

¹ There are no capital costs or operating and maintenance costs associated with this information collection.



VII. References

The following references have been placed on display at the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Mullen, P. D., and L. W. Green,
"Measuring Patient Drug Information Transfer:
An Assessment of the Literature,"
Pharmaceutical Manufacturers Association,
Washington, DC, 1983.
2. Kanouse, D. E. et al., "Informing
Patients About Drugs: Summary Report on
Alternative Designs for Prescription Drug
Leaflets," Rand Corp., Santa Monica, CA,
1981.
3. Morris, L. A., M. Mazis, and E.
Gordon, "A Survey of the Effects of Oral
Contraceptive Patient Information, Journal of
the American Medical Association, 238(23),
2504-2508, 1977.
4. Gibbs, S., W. E. Waters, and C. F.
George, "The Benefits of Prescription
Information Leaflets (2)," British Journal of
Clinical Pharmacology, 28:345-351, 1989.
5. Guarino, R., "PPI: The Proper
Prescription?" Food Drug and Cosmetic Law
Journal, 34:116, 1979.

6. Howland, S., M. G. Baker, and T. Poe, "Does Patient Education Cause Side Effects? A Controlled Trial," The Journal of Family Practice, 31:62-64, 1990.

7. Lamb, G. C., S. S. Green, and J. Heron, "Can Physicians Warn Patients of Potential Side Effects Without Fear of Causing Those Side Effects?" Archives of Internal Medicine, 154:2753-2756, 1994.

8. Morris, L. A., and D. E. Kanouse, "Informing Patients About Drug Side Effects," Journal of Behavioral Medicine, 5:363-373, 1982.

9. Docket No. 93N-0371.

10. Morris, L. A. et al., "Patient Receipt of Prescription Drug Information," National Technical Information Service, No. PB84-100031, 1984, Springfield, VA.

11. Morris, L. A. et al., "A National Survey of Prescription Drug Information Provided to Patients," National Technical Information Service, No. PB86-186947/XAB, 1986, Springfield, VA.

12. Morris, L. A., A. M. Myers, and D. G. Thilman, "Application of the Readability Concept to Patient-oriented Drug

Information," American Journal of Hospital Pharmacy, 37:1504-1509, 1980.

319. Morris, L. A., and D. Kanouse,
"Consumer Reactions to the Tone of Written
Drug Information," American Journal of
Hospital Pharmacy, 38:667-671, 1981.

14. Morris, L. A., M. Hastak, and M.
Mazis, "Consumer Comprehension of
Environmental Advertising and Labeling
Claims," Journal of Consumer Affairs, 29:
328-350, 1995.

15. Morris, L. A., and D. Kanouse,
"Consumer Reactions to Differing Amounts of
Written Drug Information," Drug Intelligence
and Clinical Pharmacy, 14:531-536, 1980.

16. Backinger, C. L., and P. A.
Kingsley, "Write It Right: Recommendations
for Developing User Instructions for Medical
Devices Used in Home Health Care," Department
of Health and Human Services, Publication No.
FDA 93-4258, 1993.

17. Doak, C. C., L. G. Doak, and J. H.
Root, "Teaching Patients with Low Literacy
Skills," Philadelphia, J. B. Lippincott Co.,
1985.

OTR
Ann
Hester
my

18. Felker, D. B. et al., "Guidelines for Document Designers," Washington, DC, American Institutes for Research, 1981.

19. Mettger, W., and J. Mara, "Clear and Simple: Developing Print Materials for Low-Literacy Readers," Bethesda, MD, National Cancer Institute, 1992.

20. Nonprescription Drug Manufacturers Association, "Label Readability Guidelines," Washington, DC.

21. Koberstein, W., "Reach the People: The Progress of Direct-to-Consumer Communications," Pharmaceutical Executive, 7: 36-58, July 1993.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 208

Drugs, Patient labeling, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 610

Biologics, Labeling, Reporting and Recordkeeping requirements.

1-24-98
ann haw
my

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Chapter I of Title 21 of the Code of Federal Regulations is amended to read as follows:

PART 201--LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.57 is amended by revising paragraph (f)(2) to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

* * * * *

(f) * * *

(2) Information for patients: This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in

§ 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

* * * * *

3. Part 208 is added to read as follows:

PART 208--MEDICATION GUIDES FOR PRESCRIPTION DRUG PRODUCTS

Subpart A--General Provisions

Sec.

208.1 Scope and purpose.

208.3 Definitions.

Subpart B--General Requirements for a Medication Guide

208.20 Content and format of a Medication Guide.

208.24 Distributing and dispensing a Medication Guide.

208.26 Exemptions and deferrals.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360, 371, 374; 42 U.S.C. 262.

Subpart A--General Provisions

§ 208.1 Scope and purpose.

(a) This part sets forth requirements for patient labeling for human prescription drug products, including biological products, that the Food and Drug Administration (FDA) determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information. It applies primarily to human prescription drug products used on an outpatient basis without direct supervision by a health professional. This part shall apply to new prescriptions and refill prescriptions.

(b) The purpose of patient labeling for human prescription drug products required under this part is to provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products.

(c) Patient labeling will be required if the FDA determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

§ 208.3 Definitions.

For the purposes of this part, the following definitions shall apply:

(a) Authorized dispenser means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to provide drug products on prescription in the course of professional practice.

(b) Dispense to patients means the act of delivering a prescription drug product to a patient or an agent of the patient either:

(1) By a licensed practitioner or an agent of a licensed practitioner, either directly or indirectly, for self-administration by the patient, or the patient's agent, or outside the licensed practitioner's direct supervision; or

(2) By an authorized dispenser or an agent of an authorized dispenser under a lawful prescription of a licensed practitioner.

(c) Distribute means the act of delivering, other than by dispensing, a drug product to any person.

(d) Distributor means a person who distributes a drug product.

(e) Drug product means a finished dosage form, e.g., tablet, capsule, or solution, that contains an active drug ingredient, generally, but not necessarily, in association with inactive ingredients. For purposes of this part, drug product also means biological product within the meaning of section 351(a) of the Public Health Service Act.

(f) Licensed practitioner means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to prescribe drug products in the course of professional practice.

(g) Manufacturer means for a drug product that is not also a biological product, both the manufacturer as described in § 201.1 and the applicant as described in § 314.3(b) of this

chapter, and for a drug product that is also a biological product, the manufacturer as described in § 600.3(t) of this chapter.

(h) Medication Guide means FDA-approved patient labeling conforming to the specifications set forth in this part and other applicable regulations.

(i) Packer means a person who packages a drug product.

(j) Patient means any individual, with respect to whom a drug product is intended to be, or has been, used.

(k) Serious risk or serious adverse effect means an adverse drug experience, or the risk of such an experience, as that term is defined in §§ 310.305, 312.32, 314.80, and 600.80 of this chapter.

Subpart B--General Requirements for a Medication Guide
§ 208.20 Content and format of a Medication Guide.

(a) A Medication Guide shall meet all of the following conditions:

(1) The Medication Guide shall be written in English, in nontechnical, understandable language, and shall not be promotional in tone or content.

(2) The Medication Guide shall be scientifically accurate and shall be based on, and shall not conflict with, the approved professional labeling for the drug product under § 201.57 of this chapter, but the language of the Medication Guide need not be identical to the sections of approved labeling to which it corresponds.

(3) The Medication Guide shall be specific and comprehensive.

(4) The letter height or type size shall be no smaller than 10 points (1 point = 0.0138 inches) for all sections of the Medication Guide, except the manufacturer's name and address and the revision date.

(5) The Medication Guide shall be legible and clearly presented. Where appropriate, the Medication Guide shall also use boxes, bold or underlined print, or other highlighting techniques to emphasize specific portions of the text.

(6) The words "Medication Guide" shall appear prominently at the top of the first page of a Medication Guide. The verbatim statement "This Medication Guide has been approved by the U.S. Food and Drug Administration" shall appear at the bottom of a Medication Guide.

(7) The brand and established or proper name of the drug product shall appear immediately below the words "Medication Guide." The established or proper name shall be no less than one-half the height of the brand name.

(b) A Medication Guide shall contain those of the following headings relevant to the drug product and to the need for the Medication Guide in the specified order. Each heading shall contain the specific information as follows:

(1) The brand name (e.g., the trademark or proprietary name), if any, and established or proper name. Those products not having an established or proper name shall be designated by

their active ingredients. The Medication Guide shall include the phonetic spelling of either the brand name or the established name, whichever is used throughout the Medication Guide.

(2) The heading, "What is the most important information I should know about (name of drug)?" followed by a statement describing the particular serious and significant public health concern that has created the need for the Medication Guide. The statement should describe specifically what the patient should do or consider because of that concern, such as, weighing particular risks against the benefits of the drug, avoiding particular behaviors (e.g., activities, drugs), observing certain events (e.g., symptoms, signs) that could prevent or mitigate a serious adverse effect, or engaging in particular behaviors (e.g., adhering to the dosing regimen).

(3) The heading, "What is (name of drug)?" followed by a section that identifies a drug product's indications for use. The Medication Guide may not identify an indication unless the indication is identified in the indications and usage section of the professional labeling for the product required under § 201.57 of this chapter. In appropriate circumstances, this section may also explain the nature of the disease or condition the drug product is intended to treat, as well as the benefit(s) of treating the condition.

(4) The heading, "Who should not take (name of drug)?" followed by information on circumstances under which the drug product should not be used for its labeled indication (its

contraindications). The Medication Guide shall contain directions regarding what to do if any of the contraindications apply to a patient, such as contacting the licensed practitioner or discontinuing use of the drug product.

(5) The heading, "How should I take (name of drug)?" followed by information on the proper use of the drug product, such as:

(i) A statement stressing the importance of adhering to the dosing instructions, if this is particularly important;

(ii) A statement describing any special instructions on how to administer the drug product, if they are important to the drug's safety or effectiveness;

(iii) A statement of what patients should do in case of overdose of the drug product; and

(iv) A statement of what patients should do if they miss taking a scheduled dose(s) of the drug product, where there are data to support the advice, and where the wrong behavior could cause harm or lack of effect.

(6) The heading "What should I avoid while taking (name of drug)?" followed by a statement or statements of specific, important precautions patients should take to ensure proper use of the drug, including:

(i) A statement that identifies activities (such as driving or sunbathing), and drugs, foods, or other substances (such as tobacco or alcohol) that patients should avoid when using the medication;

(ii) A statement of the risks to mothers and fetuses from the use of the drug during pregnancy, if specific, important risks are known;

(iii) A statement of the risks of the drug product to nursing infants, if specific, important risks are known;

(iv) A statement about pediatric risks, if the drug product has specific hazards associated with its use in pediatric patients;

(v) A statement about geriatric risks, if the drug product has specific hazards associated with its use in geriatric patients; and

(vi) A statement of special precautions, if any, that apply to the safe and effective use of the drug product in other identifiable patient populations.

(7) The heading, "What are the possible or reasonably likely side effects of (name of drug)?" followed by:

(i) A statement of the adverse reactions reasonably likely to be caused by the drug product that are serious or occur frequently.

(ii) A statement of the risk, if there is one, of patients' developing dependence on the drug product.

(8) General information about the safe and effective use of prescription drug products, including:

(i) The verbatim statement that "Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide" followed by a statement that patients should ask health

professionals about any concerns, and a reference to the availability of professional labeling;

(ii) A statement that the drug product should not be used for a condition other than that for which it is prescribed, or given to other persons;

(iii) The name and place of business of the manufacturer, packer, or distributor of a drug product that is not also a biological product, or the name and place of business of the manufacturer or distributor of a drug product that is also a biological product, and in any case the name and place of business of the dispenser of the product may also be included; and

(iv) The date, identified as such, of the most recent revision of the Medication Guide placed immediately after the last section.

(9) Additional headings and subheadings may be interspersed throughout the Medication Guide, if appropriate.

§ 208.24 Distributing and dispensing a Medication Guide.

(a) The manufacturer of a drug product for which a Medication Guide is required under this part shall obtain FDA approval of the Medication Guide before the Medication Guide may be distributed.

(b) Each manufacturer who ships a container of drug product for which a Medication Guide is required under this part is responsible for ensuring that Medication Guides are available for distribution to patients by either:

(1) Providing Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product; or

(2) Providing the means to produce Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product.

(c) Each distributor or packer that receives Medication Guides, or the means to produce Medication Guides, from a manufacturer under paragraph (b) of this section shall provide those Medication Guides, or the means to produce Medication Guides, to each authorized dispenser to whom it ships a container of drug product.

(d) The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.

(e) Each authorized dispenser of a prescription drug product for which a Medication Guide is required under this part shall, when the product is dispensed to a patient (or to a patient's agent), provide a Medication Guide directly to each

patient (or to the patient's agent) unless an exemption applies under § 208.26.

(f) An authorized dispenser or wholesaler is not subject to section 510 of the Federal Food, Drug, and Cosmetic Act, which requires the registration of producers of drugs and the listing of drugs in commercial distribution, solely because of an act performed by the authorized dispenser or wholesaler under this part.

§ 208.26 Exemptions and deferrals.

(a) FDA on its own initiative, or in response to a written request from an applicant, may exempt or defer any Medication Guide content or format requirement, except those requirements in § 208.20(a)(2) and (a)(6), on the basis that the requirement is inapplicable, unnecessary, or contrary to patients' best interests. Requests from applicants should be submitted to the director of the FDA division responsible for reviewing the marketing application for the drug product, or for a biological product, to the application division in the office with product responsibility.

(b) If the licensed practitioner who prescribes a drug product subject to this part determines that it is not in a particular patient's best interest to receive a Medication Guide because of significant concerns about the effect of a Medication Guide, the licensed practitioner may direct that the Medication Guide not be provided to the particular patient. However, the authorized dispenser of a prescription drug product subject to this part shall provide a Medication Guide to any patient who

requests information when the drug product is dispensed regardless of any such direction by the licensed practitioner.

PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET
A NEW DRUG OR AN ANTIBIOTIC DRUG

4. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371, 374, 379e.

5. Section 314.50 is amended by revising the first and third sentences of the introductory text, paragraph (c)(2)(i), the first sentence of paragraph (d)(5)(vi)(b), paragraph (e)(2)(ii), and the fourth sentence in paragraph (k)(1) to read as follows:

11-24-98
ann
Halo
ny

§ 314.50 Content and format of an application.

Applications and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. * * * An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. * * *

* * * * *

(c) * * *

(2) * * *

(i) The proposed text of the labeling, including, if applicable, any Medication Guide required under part 208 of this chapter, for the drug, with annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling, and, if the application is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57 of this chapter.

* * * * *

(d) * * *

(5) * * *

(vi) * * *

(b) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. * * *

* * * * *

(e) * * *

(2) * * *

(ii) Copies of the label and all labeling for the drug product (including, if applicable, any Medication Guide required under part 208 of this chapter) for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

* * * * *

11-24-98
Amended
my

(k) * * *

(1) * * * Information relating to samples and labeling (including, if applicable, any Medication Guide required under part 208 of this chapter), described in paragraph (e) of this section, is required to be submitted in hard copy. * * *

* * * * *

6. Section 314.70 is amended by revising paragraph (b)(3) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(b) * * *

(3) Labeling. (i) Any change in labeling, except one described in paragraphs (c)(2) or (d) of this section.

(ii) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv).

* * * * *

7. Section 314.94 is amended by revising paragraph (a)(8) to read as follows:

§ 314.94 Content and format of an abbreviated application.

* * * * *

(a) * * *

(8) Labeling--(i) Listed drug labeling. A copy of the currently approved labeling (including, if applicable, any

Medication Guide required under part 208 of this chapter) for the listed drug referred to in the abbreviated new drug application, if the abbreviated new drug application relies on a reference listed drug.

(ii) Copies of proposed labeling. Copies of the label and all labeling for the drug product including, if applicable, any Medication Guide required under part 208 of this chapter (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) Statement on proposed labeling. A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) Comparison of approved and proposed labeling. A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such

differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

* * * * *

PART 601--LICENSING

8. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263; 15 U.S.C. 1451-1561.

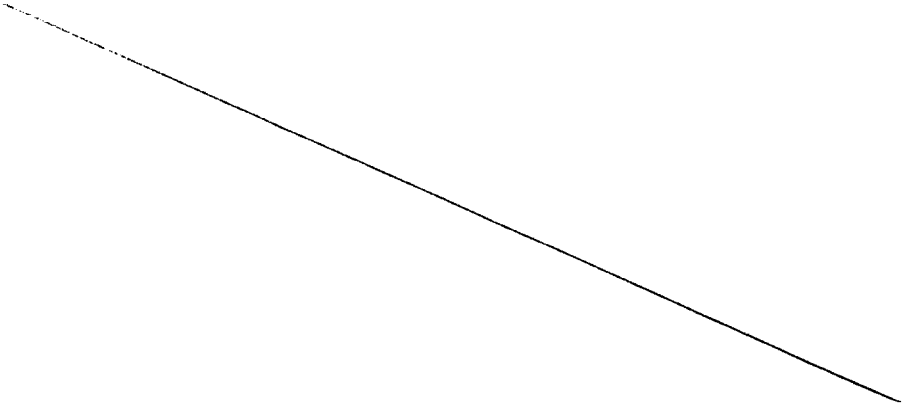
9. Section 601.2 is amended by revising the first sentence in the introductory text of paragraph (a) and paragraph (c)(1)(viii) to read as follows:

§ 601.2 Applications for establishment ^{and} product, ~~and biologics~~ licenses; procedures for filing.

(a) To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Center for Biologics Evaluation and Research, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and

11-24-98
Ann Hase
my

potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter or was not subject to such requirements in accordance with § 56.104 or § 56.105 of this chapter, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried, or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of



the labels, enclosures, containers, and, if applicable, any Medication Guide required under part 208 of this chapter proposed to be used for the product. * * *

* * * * *

(c) (1) * * *

(viii) Specimens of the labels, enclosures, containers, and, if applicable, any Medication Guide required under part 208 of this chapter proposed to be used for the product.

10. Section 601.12 ~~is~~ amended by revising the second sentence of paragraph (f) (1), and paragraph (f) (3) ⁽¹⁾ to read as follows:

11-24-98
OFK Annals
my

§ 601.12 Changes to an approved application.

* * * * *

(f) * * *

(1) * * * Except as described in paragraphs (f) (2) and (f) (3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, container label, or, if applicable, a Medication Guide required under part 208 of this chapter, and include the information necessary to support the proposed change. * * *

* * * * *

(3) * * *

(i) An applicant shall submit any final printed package insert, package label, container label, or Medication Guide required under part 208 of this chapter incorporating the

following changes in an annual report submitted to FDA each year as provided in paragraph (d)(1) of this section:

- (A) Editorial or similar minor changes;
- (B) A change in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form; and
- (C) A change in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter for a Medication Guide.

* * * * *

PART 610--GENERAL BIOLOGICAL PRODUCTS STANDARDS

11. The authority citation for 21 CFR part 610 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

12. Section 610.60 is amended by adding paragraph (a)(7) to read as follows:

§ 610.60 Container label.

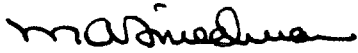
(a) * * *

(7) If a Medication Guide is required under part 208 of this chapter, the statement required under § 208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed

and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label.

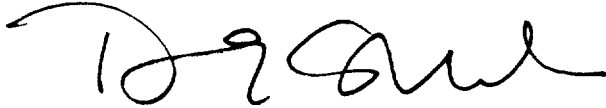
Dated: 4/21/98

April 21, 1998



Michael A. Friedman,
Lead Deputy Commissioner for the
Food and Drug Administration.

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL



Donna E. Shalala,
Secretary of Health and Human Services.